HAEMATOLOGICAL ABNORMALITIES IN DECOMPENSATED CHRONIC LIVER DISEASE

Dissertation submitted to
THE TAMIL NADU Dr.M.G.R. MEDICAL UNIVERSITY
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With partial fulfillment of the regulations
for the award of the degree of

M.D. GENERAL MEDICINE
BRANCH – I

DEPARTMENT OF INTERNAL MEDICINE

TIRUNELVELI MEDICAL COLLEGE

TIRUNELVELI –627011

TAMIL NADU

INDIA

APRIL 2013

CERTIFICATE

This is to certify that this dissertation entitled "**HAEMATOLOGICAL ABNORMALITIES IN DECOMPENSATED CHRONIC LIVER DISEASE"** is a bonafide original work of Dr FAEEZ MOHAMAD ALIin partial fulfillment of the requirement for M.D. (Branch-I) General Medicine Examination of the Tamil Nadu Dr.M.G.R Medical University, Chennai, to be held in April 2013.

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This is to certify that the Institutional Ethical Committee of this College unanimously approves the Thesis /Dissertation/ Research Proposal submitted before this committee by Dr. FAEEZ MOHAMAD ALI, a **POSTGRADUATE IN GENERAL MEDICINE** in the Department of **GENERAL MEDICINE**, of Tirunelveli Medical College /Hospital, Tirunelveli titled **"HAEMATOLOGICAL ABNORMALITIES IN THE DECOMPENSATED LIVER DISEASE"** registered by the IEC as 088/G.M/IEC/2011 dated. 12.8.**2011**. The Investigator is hereby advised to adhere to all the stipulated norms and conditions of this ethical committee.

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DECLARATION

I solemnly declare that this dissertation entitled "**HAEMATOLOGICAL ABNORMALITIES IN DECOMPENSATED CHRONIC LIVER DISEASE**" is a bonafide record of work done by me in the Department of General Medicine at Tirunelveli Medical College Hospital from 2010 to 2013 under the guidance and supervision of PROF. DR. R. GEETHRANI M.D. This dissertation is submitted to Tamil Nadu Dr.M.G.R. Medical University in partial fulfillment of the University regulations for the award of M.D. (BRANCH – I) General Medicine degree examination to be held in April 2013.

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DATE:

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ABBREVIATIONS

CLD	:	Chronic liver disease
DCLD	:	Decompensated Chronic liver disease
PT – INR	:	Prothrombin time – International Normalized Ratio
APTT	:	Activated partial thromboplastin time
Hb	:	Haemoglobin
MCV	:	Mean Corpuscular Volume
MCH	:	Mean Corpuscular Haemoglobin
MCHC	:	Mean Corpuscular Haemoglobin Concentration
PCV	:	Packed Cell Volume
TC	:	Total Count
DC	:	Differential Count
DIC	:	Disseminated Intravascular Coagulation
RBC	:	Red Blood Cell
WBC	:	White Blood Cell
Fe	:	Iron
TNF-α	:	Tumor Necrosis Factor Alpha
TIBC	:	Total Iron Binding Capacity
HDL	:	High Density Lipoprotein
CT Scan	:	Computerized Tomography
HBV Ag	:	Hepatitis B Virus Antigen
HCV	:	Hepatitis C Virus

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CONTENTS

INTRODUCTION

"Is life worth living? It all depends on the liver " quoted the well known American philosopher William James (1842 – 1910)

The liver is the largest organ in the body[1] and one of the most complex functioning organs with a wide array of functions.

It plays a major role in carbohydrate, protein, lipid metabolism; inactivation of various toxins, metabolism of drugs, hormones, synthesis of plasma proteins & maintenance of immunity (Kupffer cells).

Right from being a primary site of haematopoiesis in fetal life to maintenance of hematological parameters in postnatal life; the liver has an extremely important role in maintenance of blood homeostasis.

It acts as a storage depot for Iron, Folic acid & Vitamin B12, secretes clotting factors and inhibitors. Hence it's not surprising to see a wide range of hematological abnormalities in liver diseases.

In chronic liver disease the presence of jaundice, liver cell failure, portal hypertension and hypersplenism, reduced red cell half- life all influence peripheral blood picture[2]. Both Liver cell failure & cholestasis can derange the coagulation system. Dietary deficiencies, bleeding, alcoholism and abnormalities in hepatic synthesis of proteins used for blood formation or coagulation add to the problem liver disease[3].

This study was undertaken to describe the hematological abnormalities in decompensated chronic liver disease so that measures could be taken to correct them and reduce morbidity.

AIM OF THE STUDY

1. To assess the hematological abnormalities in decompensated chronic liver disease
2. To detect RBC abnormalities in patients with decompensated chronic liver disease
3. To determine severity, morphology & most common type of anemia in chronic liver disease.
4. To perform iron studies and to determine the most common type of anemia. To correlate ferritin and transferrin levels with the severity of liver disease.
5. To determine folic acid levels in cirrhosis
6. To determine Vitamin B12 levels and correlate with the severity of liver disease
7. Quantitatively assess WBC abnormalities
8. To detect platelet abnormalities in decompensated chronic liver disease
9. To assess the coagulation profile of patients with decompensated chronic liver disease.

REVIEW OF LITERATURE

The liver is the largest organ in the body comprising 1/50th of the total adult body weight[4]. The median liver weight is 1,800 g in men and 1,400 g in women[5]. It is relatively larger in infants being about 1/18th of the total body weight. Sheltered by the ribs in the right upper quadrant, it consists of two anatomical lobes – right and left, the right lobe being about 6 times larger than the left.

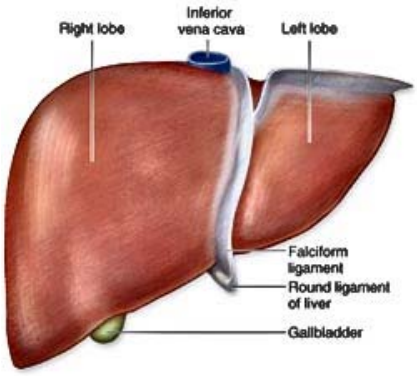


Figure 1: ANATOMICAL LOBES OF LIVER

The liver has a dual blood supply[6] – the portal vein rich in nutrients brings venous blood from the intestines and spleen. The hepatic artery, a branch of the celiac axis supplies oxygen rich blood to the parenchyma. A functional anatomy is recognized based upon vascular and biliary anatomy. The Couinaud classification[7] defines eight segments while the Bismuth classification[8] defines 4 sectors. Using this definition the functional right and left lobes are divided by a plane running through the gall bladder fossa inferiorly and the groove for the IVC posteriorly.The main portal vein divides into right and left branches and each gives a branch to the 8 functional segments.

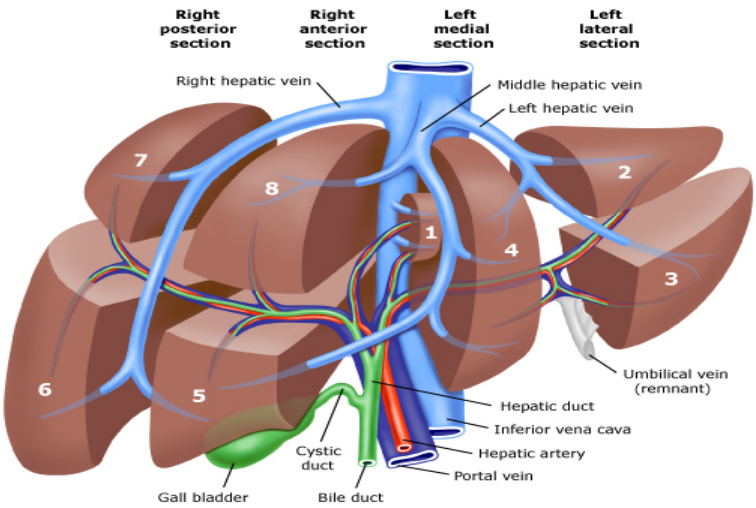


Figure 2: COUINAUDS SEGMENTS OF LIVER

The right anterior sector contains segments V & VIII, the right posterior sector VI & VII. The left lateral sector contains segments II & III, the left medial sector being segment IV. Segment I the equivalent of the caudate lobe does not derive blood directly from the major portal branches or drain by any of the 3 major hepatic veins. This functional classification allows interpretation of radiological data and is of importance to the surgeon planning a liver resection.

MICROANATOMY OF THE LIVER

There are approximately 202 * 10^3 cells in each mg of normal human liver, of which 171 * 10^3 is parenchymal and 31 * 10^3 littoral (sinusoidal including Kupffer cells) [9]. Many models of liver substructure have been proposed, the most popular of these is the hepatic lobule by Kiernan[10] in 1883. He described circumscribed hexagonal lobules centered on the terminal vein with cords of hepatocytes radiating out to the portal tracts located at each pole.

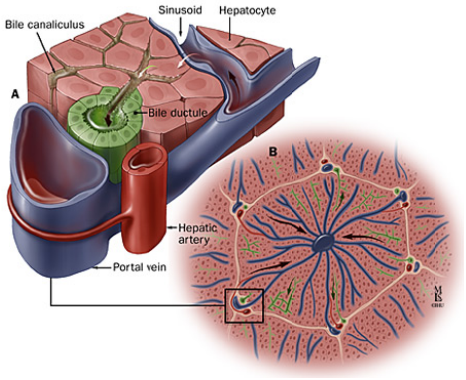


Figure 3: HEPATIC LOBULE

Rappaport[11] envisaged a series of functional acini each centered on the portal tract. The acinus occupies adjacent sectors of neighboring hexagonal fields.

The various zones 1, 2, 3 represent areas supplied with blood of first, second and third quality with regard to oxygen and nutrient content. Zone 1 received most oxygen and nutrient rich blood whereas zone 3 receives the least. Hence hepatocytes in zone 3 (perivenular) are more prone to anoxic injury.

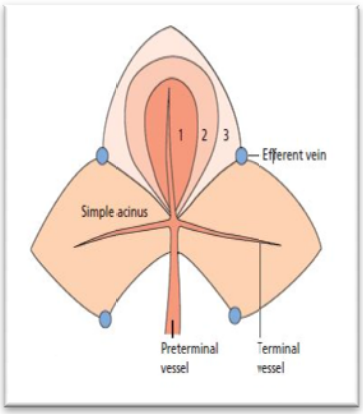


Figure 4: RAPPAPORT COMPLEX ACINUS

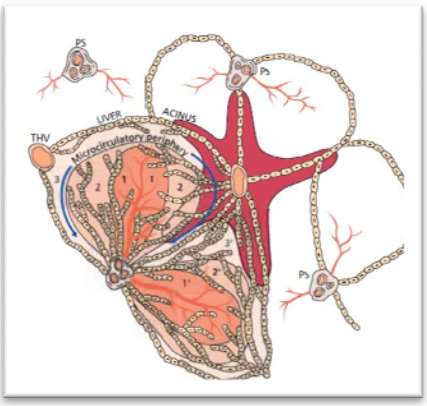


Figure 5: BLOOD SUPPLY & ZONES

FUNCTIONS OF THE LIVER

Impressed by the molding against adjacent organs, William Osler quipped that the liver was present only for packing purposes[12]!

Quite the contrary, the liver being the largest organ in the body is also the most versatile and functionally heterogeneous organ with a wide array of functions absolutely essential for life.

Table 1: FUNCTIONS OF LIVER[13]

1. Formation & secretion of bile 2. Nutrient and vitamin metabolism - Glucose and other sugars - Amino acids - Lipids: fatty acids, cholesterol, lipoproteins - Fat soluble vitamins - Water soluble vitamins 3. Inactivation of various substances - toxins - drugs - steroids - other hormones - urea cycle	4. Storage function - Glycogen storage - Lipid storage - B12 and folate storage - Fat & water soluble vitamins 5. Synthesis of plasma proteins - Acute phase proteins - Albumin - Clotting factors - Steroid binding and other hormone binding proteins - Fibrinogen, alpha-1 antitrypsin, ceruloplasmin, Haptoglobins & Complement system 6. Immunity - Kupffer cells - Immunoglobulin – IgG, IgA, IgM - Complement system

CIRRHOSIS

Cirrhosis is the end result of the fibrogenesis that occurs with chronic liver injury/disease. It is defined anatomically as a diffuse process with fibrosis and nodule formation, characterized by 3 main morphological features[14]

- Bridging fibrous septa connecting portal tracts with one another and with the terminal hepatic veins.
- Parenchymal nodules representing regenerating nodules of hepatocytes
- Disruption of liver architecture

In clinical terms cirrhosis may be described as being decompensated or compensated[15]

Compensated Cirrhosis:

Many patients are found to have abnormal liver tests during routine medical or preoperative examinations; the liver test abnormalities being relatively minor. On physical examination the detection of an unexpected hepatomegaly or splenomegaly may trigger further investigations.

Decompensated Cirrhosis:

Decompensation means cirrhosis complicated by one or more of the following features: jaundice, ascites, hepatic encephalopathy or bleeding varices. Ascites is usually the first sign. Hepatorenal syndrome, hyponatremia and spontaneous bacterial peritonitis are also features of Decompensation but in these patients ascites invariably occurs first.

This clinical distinction has major implications for prognosis and treatment. Compensated cirrhosis has 50% survival at 10 years compared to 50 % survival at 18 months for decompensated cirrhosis[16].

CHRONIC LIVER DISEASE

Liver disease lasting for more than 6 months is called chronic liver disease manifesting pathologically as cirrhosis.

AETIOLOGY-

CIRRHOSIS

Table 2: Causes of cirrhosis[17]

• Alcoholic cirrhosis • Post necrotic / post infective HCV, HBV, HBV & HDV • Non alcoholic steatohepatitis • Autoimmune hepatitis • Biliary tract diseases – primary biliary cirrhosis, secondary biliary cirrhosis, primary sclerosing cholangitis etc. • Metabolic disorders: - Wilsons disease - Hemochromatosis - Alpha 1 Anti Trypsin deficiency - Glycogen storage diseases - Cystic fibrosis - Galacatosemia - Hereditary fructose intolerance - Hereditary tyrosinemia - Ornithine transcarboymylase deficiency	• Cardiac cirrhosis • Chronic Budd Chiari syndrome • Veno-occlusive disease • Sarcoidosis • Indian Childhood cirrhosis

PATHOGENESIS

The hepatic stellate cell is the principal cell involved in fibrogenesis[18]. Normally they lie within the space of Disse and are vitamin A storing cells. With sustained injury due to any cause, under the influence of various cytokines it transforms into a myofibroblast like cell which lays down type I & III collagen in the space of Disse and periportal areas. Continued injury leads to perpetual deposition of collagen and fibrosis accompanied by regeneration of hepatocytes in the form of regenerative nodules surrounded by fibrous scars resulting in cirrhosis.

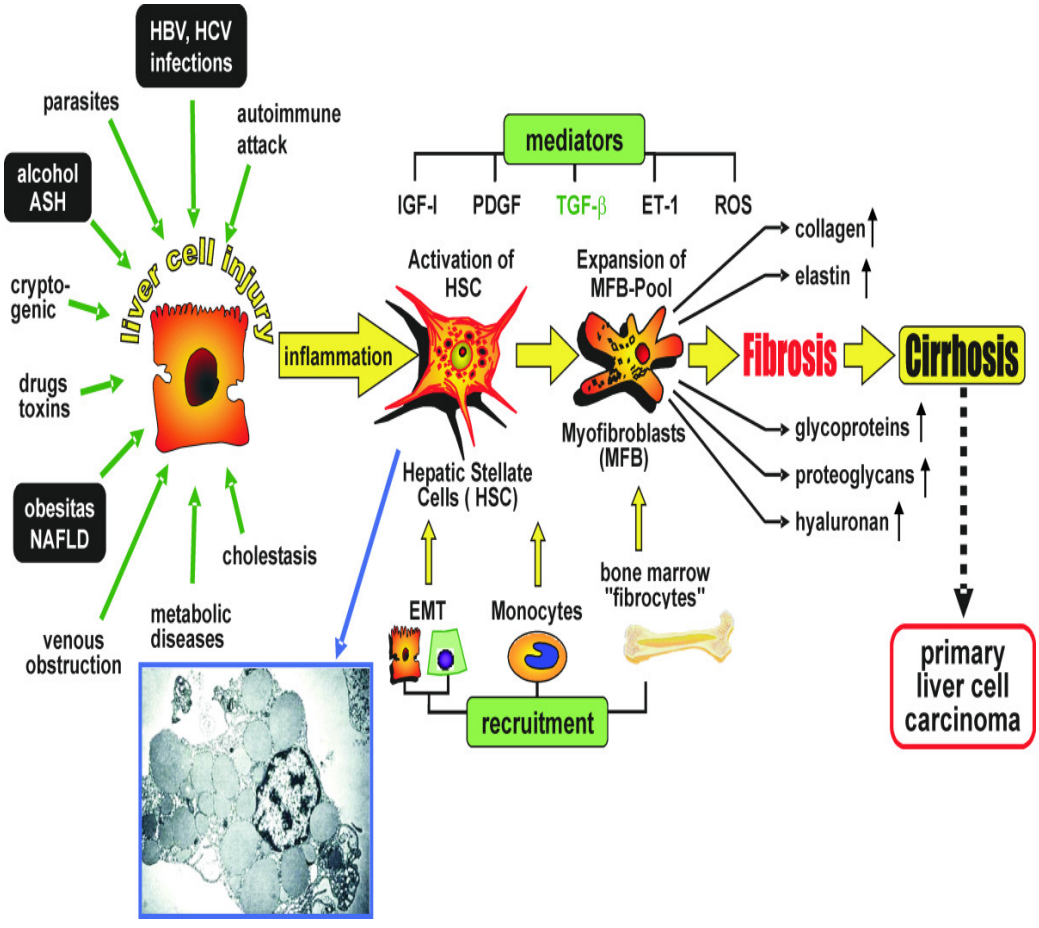


Figure 6: Hepatic Fibrogenesis[19]

CLINICAL EFFECTS OF CIRRHOSIS

The Clinical manifestations of chronic liver disease are due to portal hypertension and liver cell failure[20].

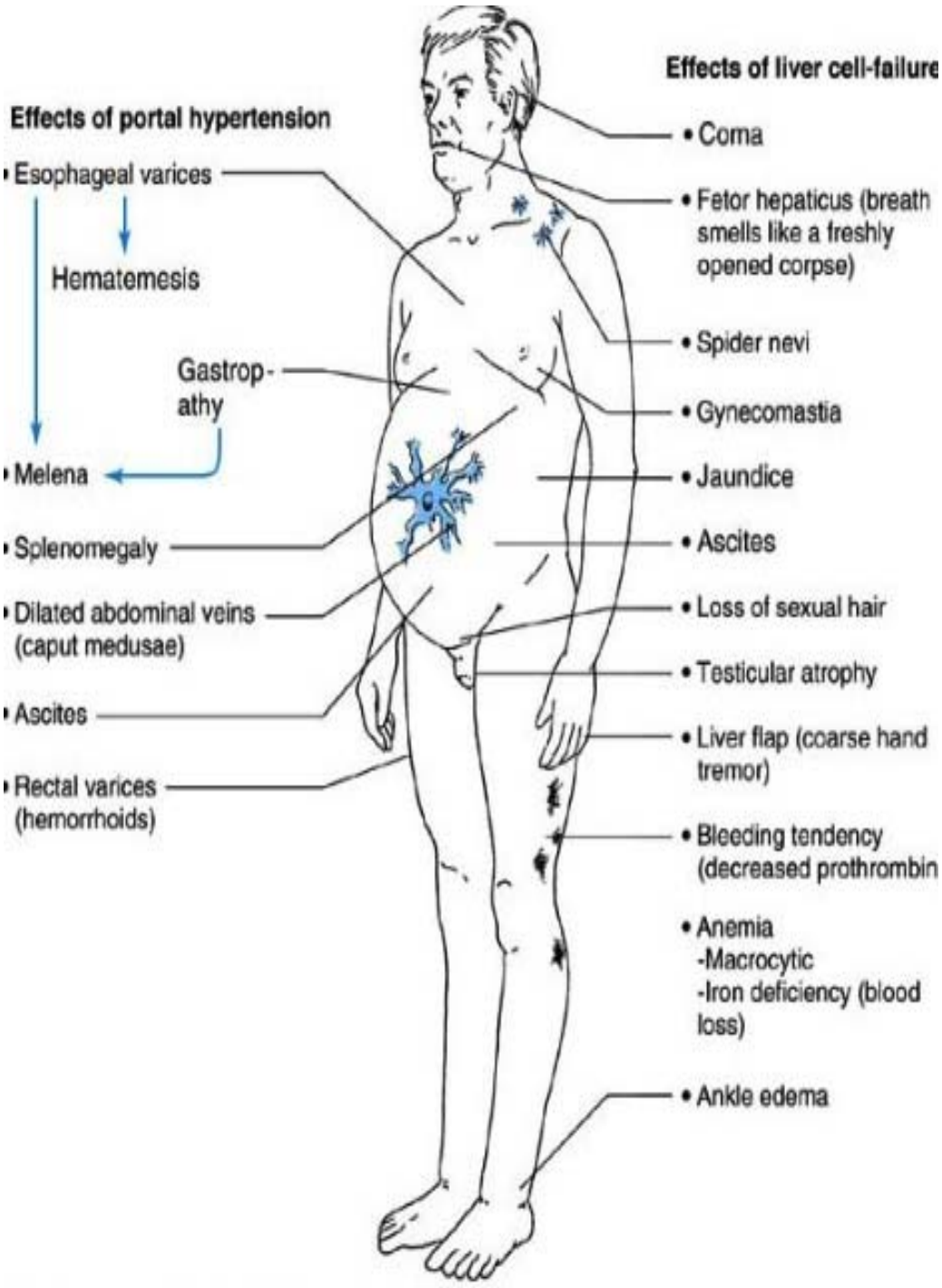


Figure 7: Clinical effects of Cirrhosis: courtesy[21] Elsevier 2006

Table 3: STIGMATA OF CHRONIC LIVER DISEASE[22]

FACE	**ENDOCRINE**
-Frontal balding	-Gynecomastia in men
-Pallor	-Breast atrophy in women
-Jaundice	-Testicular atrophy
-Parotid enlargement	-Impotence
-Madarosis	
-Xanthelasma	**FEATURES OF PORTAL**
-Telangiectasia / paper money skin	**HYPERTENSION**
-Cirrhotic facies	-Splenomegaly
-Signs of vitamin deficiencies	-Ascites
-Fetor hepaticus	-Collaterals – abdominal wall,
HANDS	esophageal, anorectal collaterals.
-Palmar erythema	
-Flapping tremor	
-Leuconychia	
-Clubbing	
-Dupytrens contractures	
SKIN	
-Bruising	
-Spider nevi	
-Scanty body hair	
-Pigmentation	
NUTRITION	
-Glossitis	
-Angular stomatitis	
-Bitot spots	
-Muscle wasting	
-Anemia	

ROLE OF THE LIVER IN HAEMATOPOIESIS

In prenatal life, the liver acts as a primary site of haematopoiesis along with the spleen. Peak hepatic haematopoiesis occurs at about the 4 to 5th month of gestation, declines thereafter and stops by the 8 to 9th month when the bone marrow takes over. In postnatal life, it continues to play a key role in supporting haematopoiesis[23]. In certain pathological states (myeloproliferative disorders, Thalassemia) the liver rekindles its role as a primary haematopioetic organ[24].

Though 85 to 90 % of the Erythropoietin is secreted from the peritubular interstitial cells of the kidney, the remaining 10 to 15 % is secreted from the liver[25]. It acts as a storage depot for folic acid and vitamin B12[26], which is necessary for RBC and WBC maturation. By secreting Transcobalamine II[27], it helps in transporting B12 from the site of absorption and storage to haematopioetic cells in the marrow. The liver plays an important role in Iron metabolism. Transferrin is an iron transporting protein secreted by the liver[28], which transports Iron from the site of absorption to the bone marrow for haemoglobin and RBC synthesis.

It regulates iron absorption by secreting Hepcidin; a molecule that down regulates Ferroportin and reduces Iron absorption; Anemia, hypoxia and low iron stores reduces Hepcidin production and thus enhances iron absorption[29].

The liver is a primary reticuloendothelial organ containing plenty of Kupffer cells, which are an intrinsic part of the innate immune system and one of the most important Antigen presenting cells.

Thrombopoietin[30] is a protein secreted by the liver that stimulates platelet synthesis.

NORMAL HAEMOSTASIS

Normal haemostasis is a tightly regulated process that maintains blood in a fluid state &permits the formation of a haemostatic clot at the site of vascular injury[31]. The pathological counterpart of haemostasis is thrombosis.

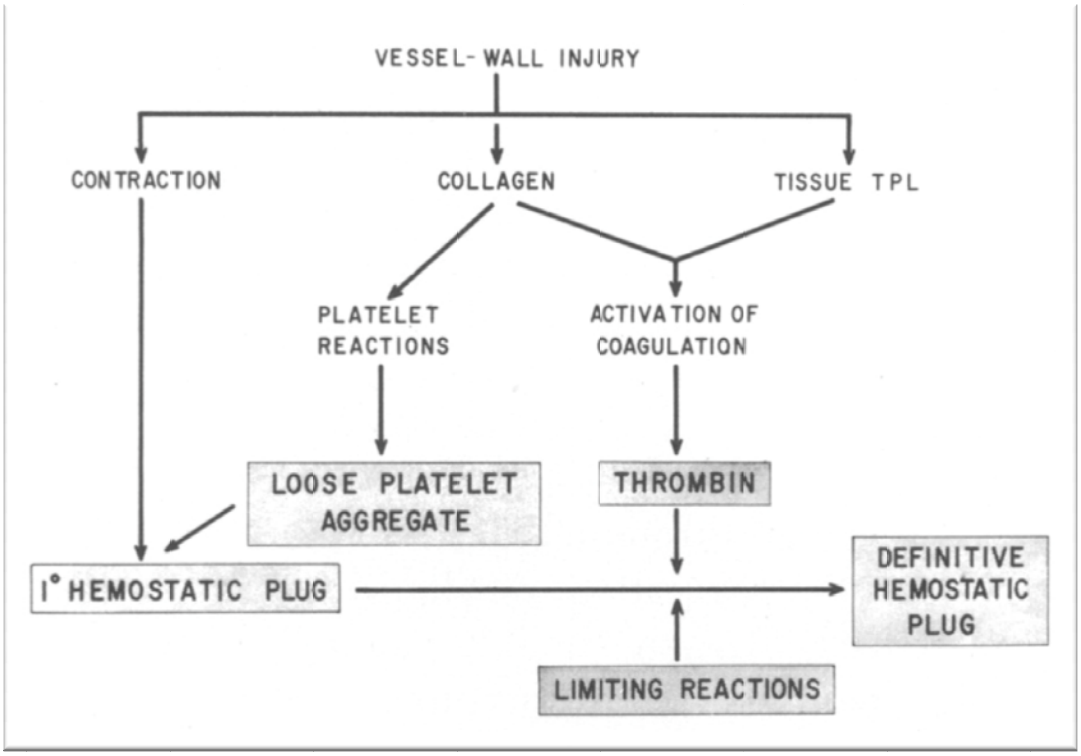


Figure 8: The Normal haemostatic sequence[32]

When a small vessel is damaged, a cascade of events is initiated that results in the formation of a temporary hemostatic plug that defends against blood loss. There is interaction between the vessel wall and platelets and not primarily the blood-coagulation mechanism[33]. This phase of haemostasis is measured with a tourniquet test and bleeding time. It is normal in patients with abnormalities of the blood clotting cascade and those receiving anticoagulant therapy. The bleeding time is abnormal in

patients with quantitative or qualitative defects in platelets or abnormalities of the vessel wall.

After initial injury there is transient arteriolar vasoconstriction[34] mediated by reflex neurogenic mechanisms & supplemented by secretion of factors such as endothelin.

- Endothelial injury exposes highly thrombogenic subendothelial collagen, causing platelet adhesion both directly and indirectly via Von Willi Brand factor. It has been established by Hovig, that when platelets are exposed to collagen, they undergo transformation[35].
- Platelet activation results in dramatic shape change (from small rounded discs to flat plates with markedly increased surface area) and the release of secretory granules. Within minutes the secreted products recruit more platelets to form the temporary primary haemostatic plug[36].

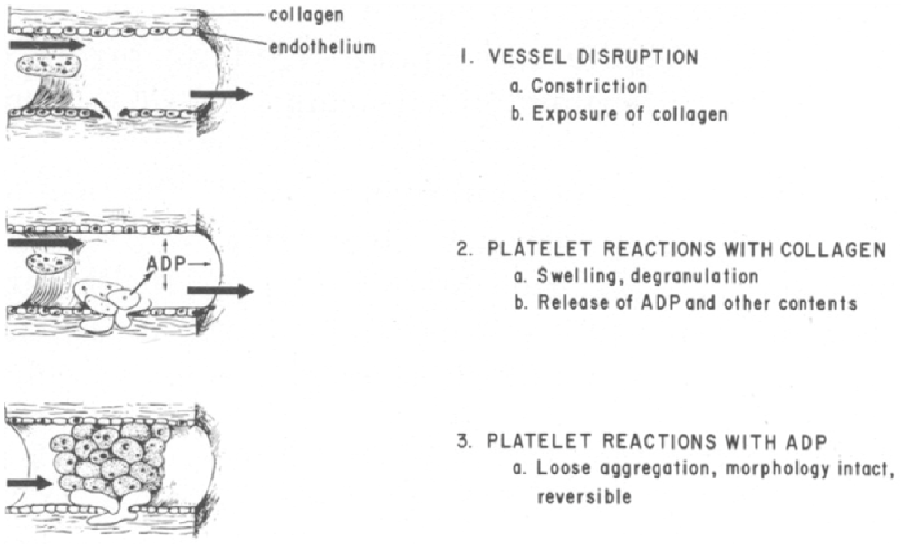


Figure 9: Primary haemostatic plug[37]

The formation of the initial temporary haemostatic plug in response to vascular damage may be visualized as a chain of events involving transient

vasoconstriction, collagen exposure, reactions between platelets and collagen, resulting in release of adenosine diphosphate and further adherence of platelets. This process continues until the vessel lumen is completely occluded by a loose, reversible aggregate of platelets. The second phase of haemostasis involves the transformation of the temporary haemostatic plug into a more permanent or definitive plug[38]. This transformation is brought about by activation of the blood-clotting cascade.

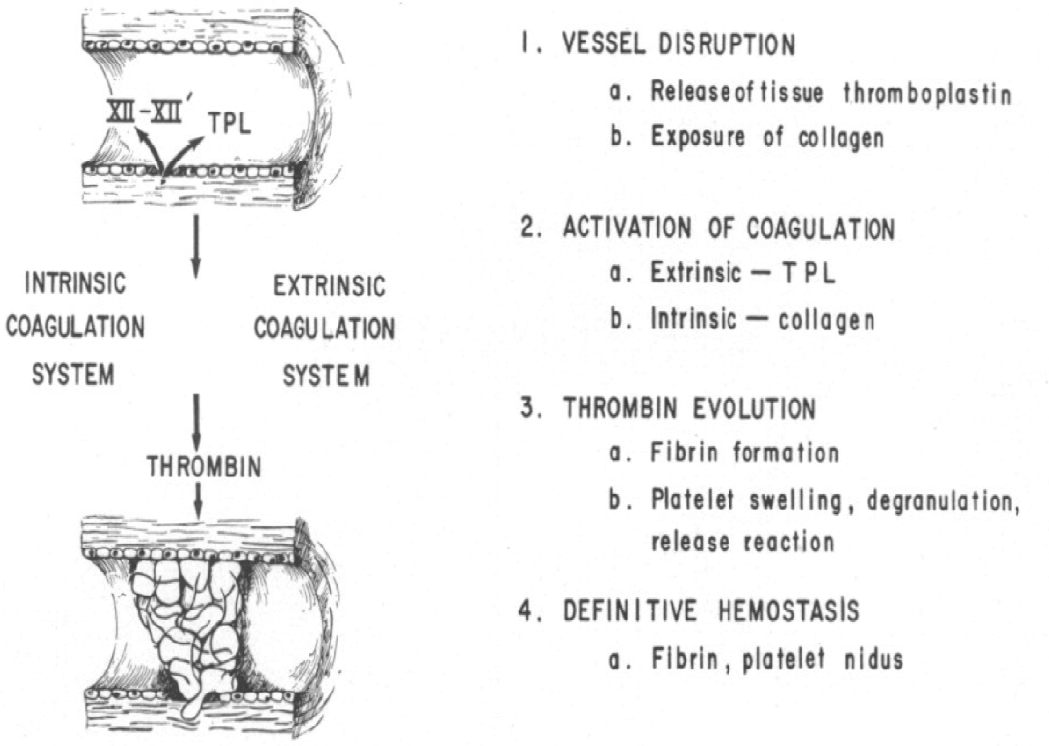


Figure 10: Secondary haemostasis[39]:

The coagulation cascade is essentially a multiplying series of enzymatic conversions[40] involving a cascade of clotting factors culminating in the formation of a definite fibrin clot. All clotting factors are synthesized in the liver except Von Willi Brand factor & Factor VIII. The vitamin K dependent factors[41] are II, VII, IX, X; these factors undergo Gamma carboxylation of glutamic acid residues to form the active molecules in the liver.

There are 2 major pathways by which prothrombin is converted to thrombin, the intrinsic and the extrinsic pathways[42].

The intrinsic pathway is initiated by the activation of the Hageman factor, or factor XII.

Wettable surface, such as glass, powdered diatoms; micelles of long chain fatty acids and collagen fibers are capable of activating the Hageman factor.

Once factor XII is activated it initiates a series of reactions in which the varying blood-clotting factors are sequentially converted from their precursor form to their active or enzymatic form.

Thus, activated factor XII activates factor XI, or plasma thromboplastin antecedent, which in turn activates factor IX, or the Christmas factor, which in turn activates factor VIII, or the antihemophilic factor. Activated factor VIII then activates factor X, known as the Stuart factor.

Activated factor X in the presence of coagulation factor V and platelet lipids converts prothrombin to thrombin.

Once thrombin is generated it converts fibrinogen to fibrin monomers, which spontaneously polymerizes. However, this polymer is weak and can easily dissociate.

Under the influence of factor XIII, this loose polymer is transformed by the formation of covalent cross-links into a dense, irreversible aggregate that is called the definitive hemostatic plug.

The extrinsic pathway is another mechanism by which prothrombin may be activated.

Many tissues like endothelium lined blood-vessel walls, lung and brain, contain a lipid-protein complex directly capable of activating factor X in the presence another cofactor called factor VII.

Activated factor X then converts prothrombin to thrombin and then follows suit, through to the final common pathway leading to the formation of the fibrin rich definitive hemostatic plug.

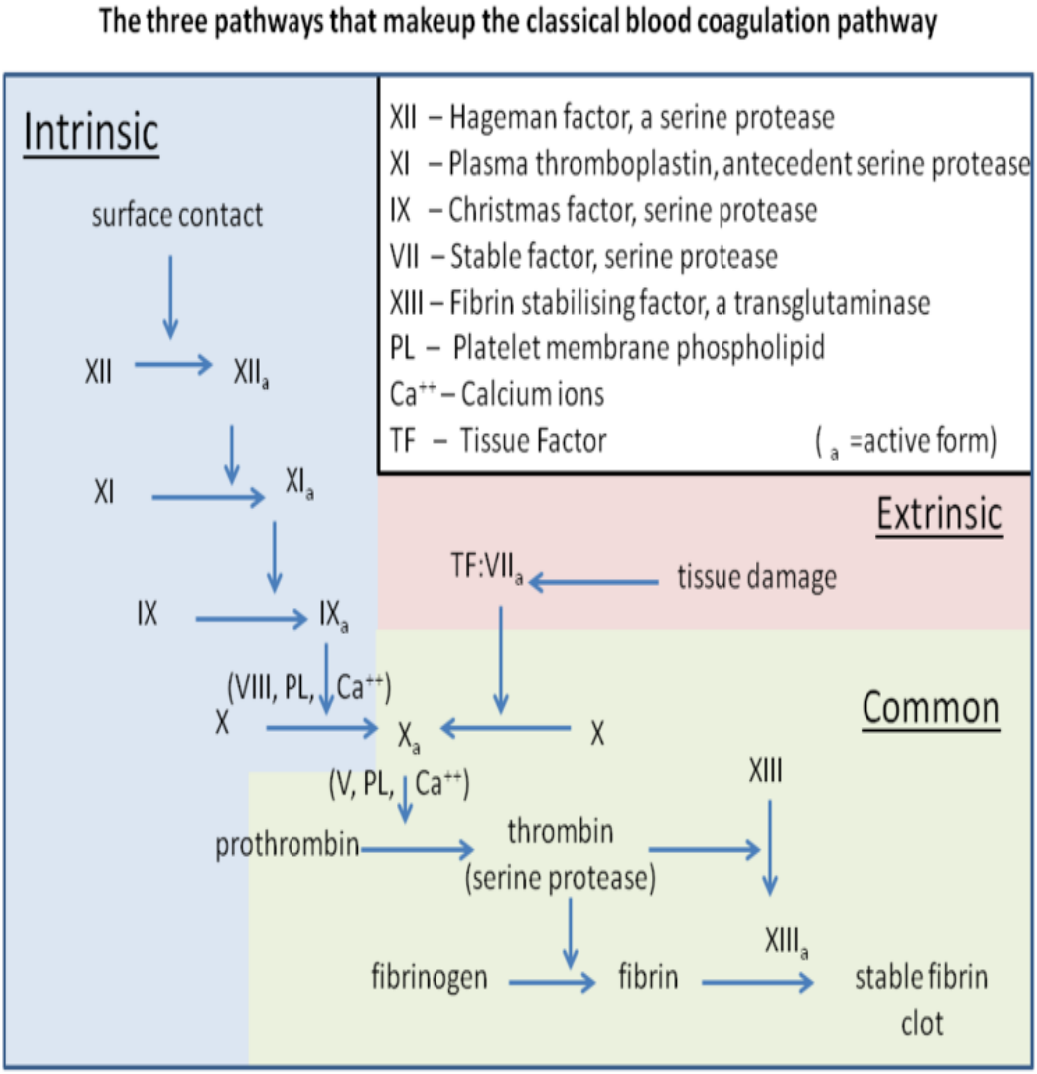


Figure 11: Coagulation cascade[43]

The functional activity of the two arms of the coagulation cascade can be measured by standardized assays[44] – The intrinsic pathway measured by Activated partial thromboplastin time, the extrinsic pathway by the Prothrombin time with INR (International normalized ratio).

The PT assay assesses the extrinsic pathway namely factors II, V, VII, X & fibrinogen. Tissue factor & phospholipids are added to citrated plasma (sodium citrate binds calcium and prevents spontaneous clotting), after which exogenous calcium is

added to the mixture to initiate clotting; the time needed for a fibrin clot to form is measured.

The Activated partial thromboplastin time assess the function of the Intrinsic pathway namely factors XII, XI, IX, VIII, X, V, II & fibrinogen. In this assay, clotting is initiated by the addition of wetting surfaces like ground glass, which then activates Hageman's factor, phospholipids and calcium& the time taken for a fibrin clot to form is noted.

Once activated, the coagulation cascade is restricted to the site of vascular damage, to prevent excessive run away clotting in the vascular compartment;
3 categories of endogenous anticoagulants[45]prevent clotting.

- Anti Thrombin III inhibits activity of thrombin and other serine proteases – IXa, Xa, XIa and XIIa. Anti thrombin III is activated by heparin like molecules and hence the action of heparin as an anticoagulant.
- Protein C & S – Vitamin K dependent endogenous anticoagulants that act in a complex that proteolytically inactivated Factor Va & VIIIa.
- TFPI – Tissue factor pathway inhibitor inactivates tissue factor – VII complexes.

Once the coagulation cascade has accomplished its mission of preventing blood loss through formation of a fibrin clot, it then sets into motion the activation of a fibrinolytic cascade[46] mediated by plasmin that cleaves the fibrin clot and restores blood flow. The resultant Fibrin degradation products most notably fibrin derived D-Dimers have weak anticoagulant activity.

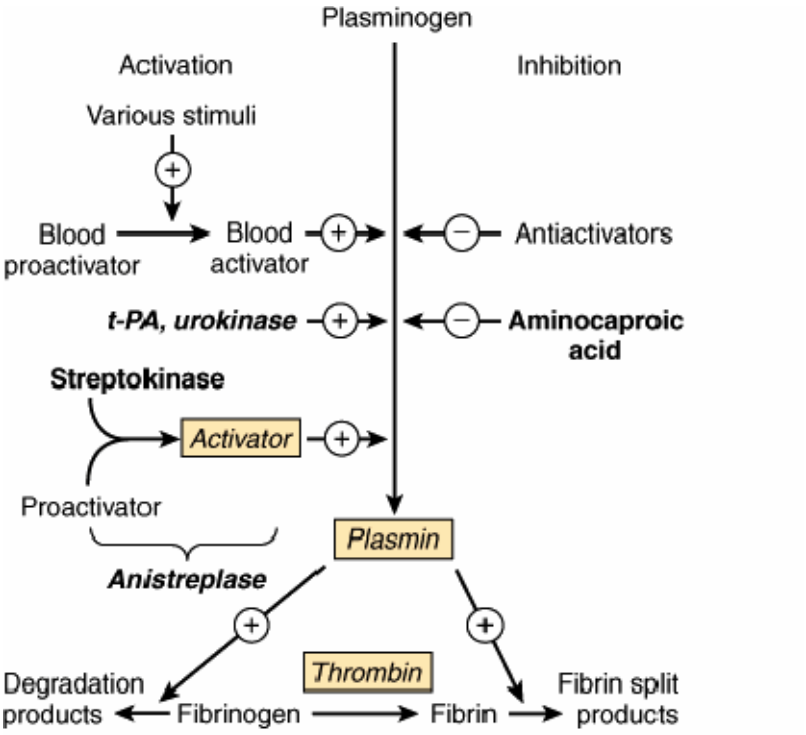


Figure 12: Fibrinolysis:[47]

Thus we see that the liver plays an essential role in all stages of haemostasis.

- Through the synthesis of Thrombopoietin, it stimulates platelet synthesis whose main function is the formation of the primary haemostatic plug.
- All clotting factors except VWF & VIII are synthesized in the liver. Activation of the clotting factors through a waterfall cascade leads to the formation of the definitive haemostatic plug.
- Liver is the site of Vitamin K storage, which is needed for the posttranslational gamma carboxylation glutamic acid residues of coagulation factors II, VII, IX & X. Vitamin K is also required for the synthesis of endogenous anticoagulants – protein C & S.I
- Inhibitors of coagulation, that is endogenous anticoagulants are also synthesized in the liver – Antithrombin III, Protein C & S.
- The liver also synthesizes plasmin inhibitors such as Alpha 2 Anti plasmin and Tissue Plasminogen Activator inhibitor.

IRON METABOLISM

An average persons diet[48] contains about 10 to 20 mg of iron, most in the form haeme contained in animal products, while remainder being inorganic iron in vegetables. About 20 % of the haeme iron is absorbable in contrast to 1 to 2 % ofnon-haeme iron.The total body iron content can be divided into functional and storage compartments.

Table 4: IRON DISTRIBUTION IN ADULTS [49]: COURTESY ROBBINS PATHOLOGY

POOL	MEN	WOMEN
TOTAL	**3450 mg**	**2450 mg**
FUNCTIONAL POOL		
HAEMOGLOBIN	**2100mg**	**1750mg**
MYOGLOBIN	**300mg**	**250mg**
ENZYMES	**50mg**	**50mg**
STORAGE POOL FERRITIN, HEMOSIDERIN	**1000mg**	**400mg**

About 80% of the functional iron is found in haemoglobin, myoglobin and iron containing enzymes such as catalase & cytochromes.

The storage pool represented by haemosiderin and ferritin contains about 15 to 20% of total body iron, females in the reproductive age having less due to menstrual blood loss. Iron in the body is recycled extensively between the functional and storage pools.

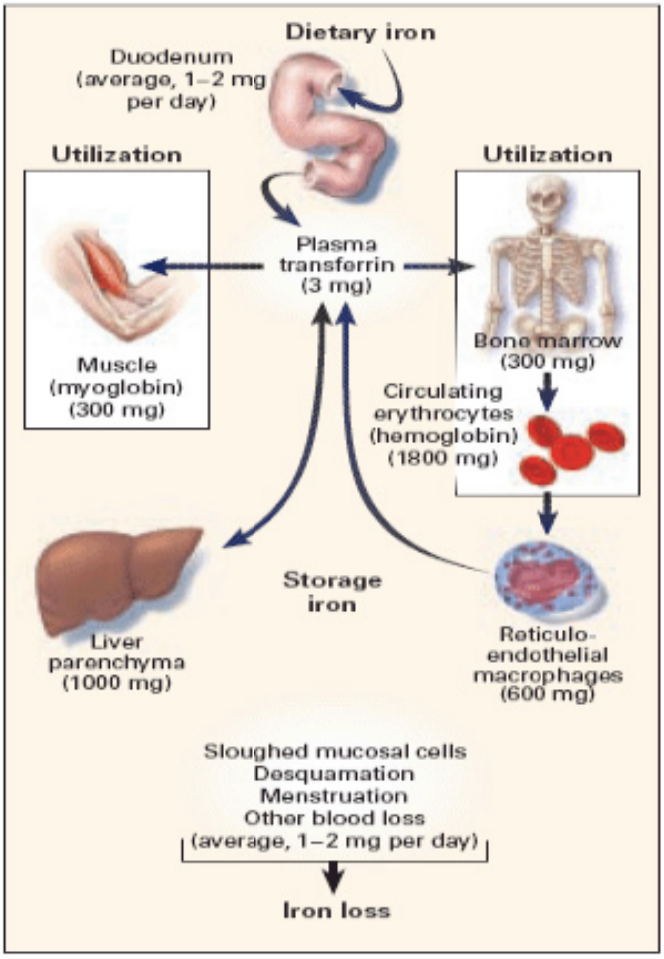


Figure 13: Iron metabolism[50]

Iron is transported in plasma by an iron-binding glycoprotein called *Transferrin*[51], which is synthesized in the liver. Normally about 1/3rd of transferrin is saturated with iron yielding an average of about 120ug/dL in men and 100ug/dL in women. The major function of plasma transferrin is to deliver iron to cells, including erythroid precursors in the bone marrow that require iron to synthesize haemoglobin[52]. Erythroid precursors possess high affinity receptors for transferrin, which mediate iron import through receptor-mediated endocytosis.

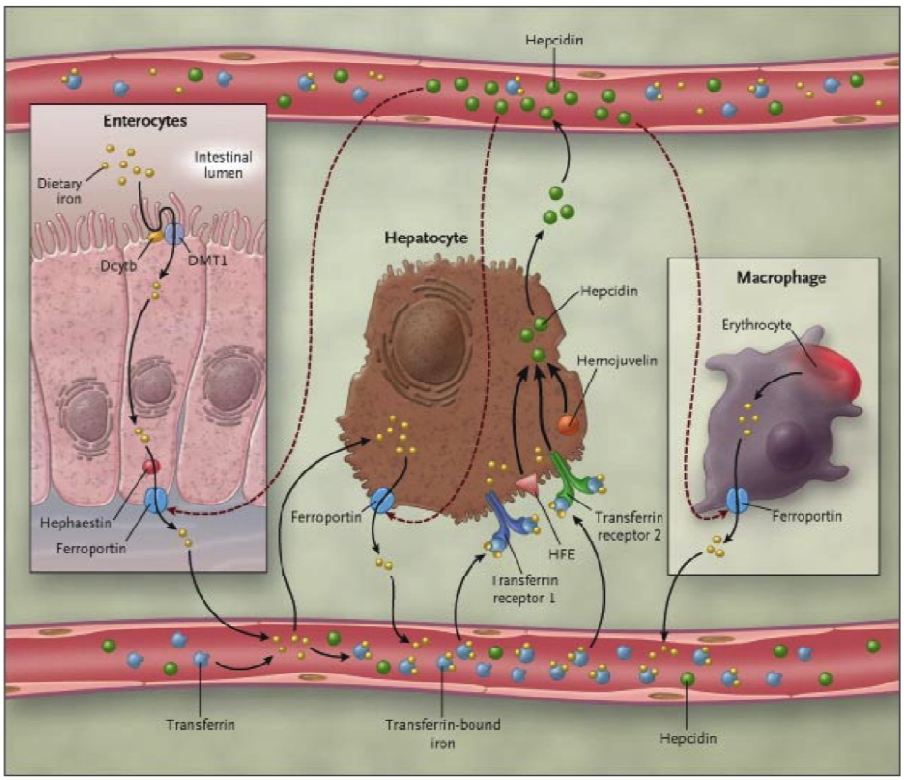


Figure 14: Iron movement from absorption to RBC synthesis[53]

Free iron is highly toxic and needs to be sequestered. This is achieved by binding iron in the storage pool to ferritin or haemosiderin.

Ferritin[54]is a ubiquitous protein-iron complex that is found at highest levels in the liver, reticuloendothelial system, and skeletal muscles. In the liver, most ferritin is

stored within the hepatocytes; in other tissues such as the spleen and bone marrow it is found mainly in macrophages.

Hepatocyte iron is derived from plasma transferrin containing ingested iron whereas macrophage iron is derived from breakdown of senescent RBCs[55].

Ferritin is stored in the cytoplasm whereas haemosiderin (aggregates of ferritin) is stored in the lysosomes. Serum ferritin levels correlate well with body iron stores.

Iron Balance is maintained largely by regulating the absorption of dietary iron in the proximal duodenum. There is no regulated pathway for iron excretion which is limited to the 1 to 2 mg lost each day through the shedding of mucosal and skin epithelial cells; in women menstrual loss contributes a large fraction.

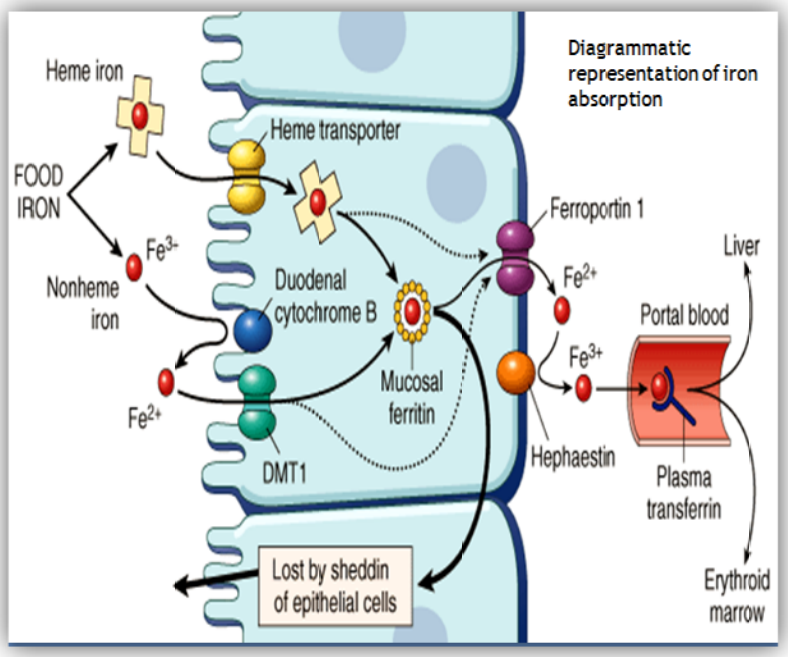


Figure 15: Absorption of dietary iron[56]

Iron absorption is regulated by *Hepcidin*[57], a small circulating peptide that is synthesized and released from the liver in response to increases in intrahepatic iron levels. Hepcidin inhibits iron transfer from the enterocyte to plasma by down

regulating Ferriportin. Hence when iron stores are adequate the liver produces more hepcidin and when iron stores are inadequate it decreases hepcidin. By inhibiting ferriportin, hepcidin not only reduces iron uptake from enterocytes but also suppresses iron uptake from macrophages, which are an important source of the iron that is used by RBC precursors to make haemoglobin. Hepcidin production is stimulated by IL-6; hence during long standing inflammation iron utilization is decreased explaining the basis of anemia of chronic disease.

Interpretation of various parameters of iron metabolism should always be done against the clinical background of the patient.

Hepatic parenchymal cells contain appreciable amounts of ferritin, and it is known that liver disease can affect the serum ferritin levels regardless of any change in iron stores.

Table 5: Iron studies interpretation[58]

	S Fe	Transf	% satn (Fe/ Transf)	Ferritin	Other features
Normal	8-34uM	2.2-3.8g/L	20-55%	20-500 ug/L	
Fe def	decr	incr	Decr(<10%)	decr	Microcytic anaemia
Chronic Disorders	decr	N, decr	decr	N, incr due to inflamn	Micro or normocytic anaemia Incr ESR or CRP
Thal, MDS	incr	N, decr	N, incr	Incr	Micro anaemia
Late preg	decr	incr	decr	decr	Decr Hb Normocytic
1)Haemochromatosis 2)Acute hepatitis	incr	decr	Incr(>70%)	Incr	1)HFE gene 2)LFTs abnormal

B12 METABOLISM

Vitamin B12 is a complex organometallic compound known as cobalamine[59]. Under normal circumstances humans are totally dependent on dietary vitamin B 12. Plants & vegetables contain little cobalamine; humans are dependent on animal sources for B12.

The daily requirement is 1 to 3 ug per day. Body stores are 2 to 3 mg, sufficient for 3 to 4 years if supplies are completely cut off[60].

- Vitamin B12 is freed from binding proteins in food through the action of pepsin in the stomach and binds to salivary proteins called haptocorrins or R Binders.
- In the duodenum, bound vitamin B12 is released by the action by the action of pancreatic proteases. It then associates with Intrinsic factor.
- This complex is transported to the ileum where it is endocytosed by ileal enterocytes through cubulin receptors.
- With ileal cells, vitamin B12 associates with a major carrier protein Transcobalamine II (synthesized by the liver)[61] and is secreted into plasma. Transcobalamine II delivers vitamin B12 to the liver and other cells of the body, including rapidly proliferating cells in the bone marrow and gastrointestinal tract.
- Between 0.5 to 5 ug of cobalamine enter the bile acid each day. This binds to IF, hence a major portion of biliary cobalamine normally is reabsorbed together with cobalamine derived from sloughed intestinal cells. Because of the appreciable amount of cobalamine undergoing enterohepatic circulation, cobalamine deficiency develops more rapidly in individuals who malabsorb

B12 than it does in vegans, in whom reabsorption of biliary cobalamine is intact.

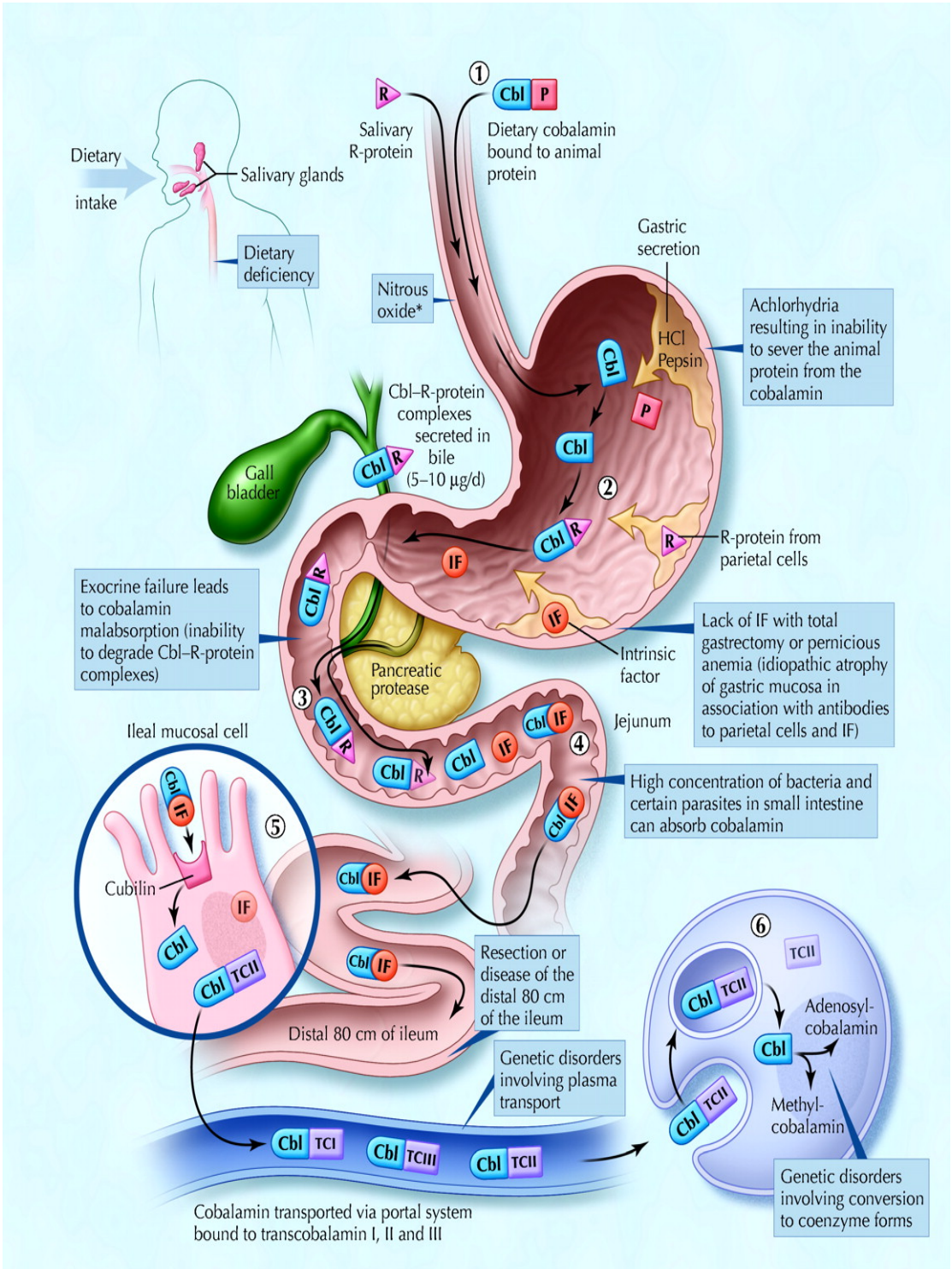


Figure 16: B12 metabolism[62]

Cobalamine exists in a number of different chemical forms. All have a cobalt atom at the centre of a corrin ring. In nature, the vitamin is mainly in the 2-deoxyadensoyl form, located chiefly in the mitochondria. It is the cofactor for the enzyme Methyl Malonyl CoA mutase. The other major natural cobalamine is methylcobalamine, the form in human plasma and in cell cytoplasm. It is the cofactor for methionine synthase.

FOLATE METABOLISM

Folic acid (also known as folate, vitamin M, pteroyl-L-glutamic acid, and pteroylmonoglutamic acid)[63] is forms of the water-soluble vitamin B_9. Folic acid is itself not biologically active, but its biological importance is due to tetrahydrofolate and other derivatives after its conversion to dihydrofolic acid in the liver.

Vitamin B_9 (folic acid and folate) is essential to numerous bodily functions. The human body needs folate to synthesize DNA, repair DNA, and methylate DNA as well as to act as a cofactor in certain biological reactions. It is especially important in aiding rapid cell division and growth, such as in infancy and pregnancy. Children and adults both require folic acid to produce healthy red blood cells and prevent anemia.

Most foods contain some folate. The highest concentrations are found in liver, yeast, spinach, other greens and nuts. The daily requirement is 100 ug and so stores are stores are sufficient only for 3 to 4 months in normal adults.

Folates act as coenzymes in the transfer of single carbon units –

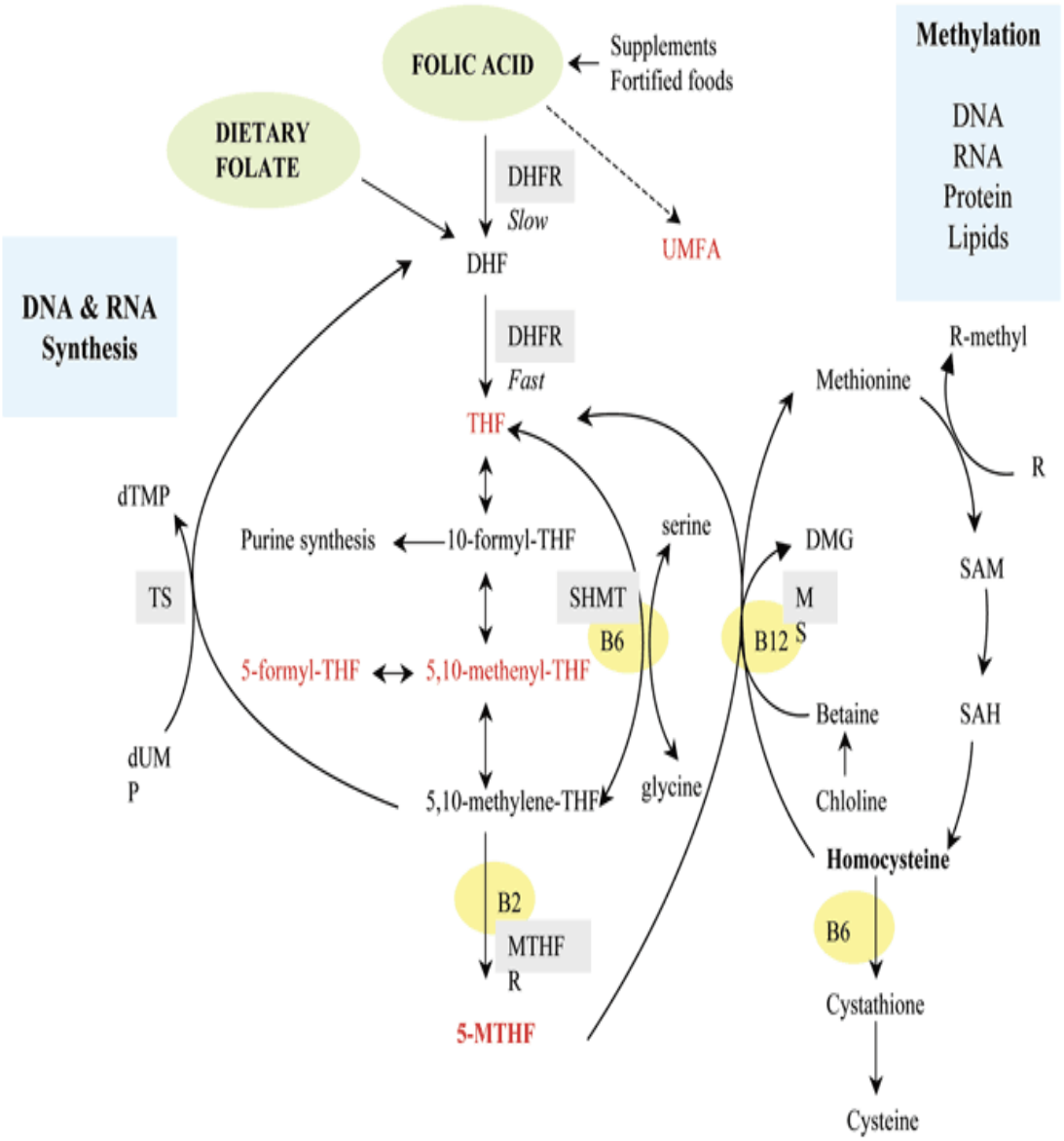


Figure 17: Biochemical functions of folate[64]

HAEMATOLOGICAL ABNORMALITIES IN CHRONIC LIVER DISEASE

Liver disease causes a large number of changes in the blood than does disease in any other organ, except the bone marrow. It serves as a primary hematopoietic organ in utero and in adult life resumes its post of haematopoiesis in certain pathological states.

BLOOD VOLUME

Plasma volume[65] is increased in patients with cirrhosis, especially with long standing moderate to severe ascites. The hypervolemia may partially, and sometimes totally account for a low peripheral haemoglobin or erythrocyte level. Total circulating haemoglobin is reduced in only about half of the patients.

ANEMIA IN CHRONIC LIVER DISEASE

Anemia occurs in up to 75% of patients with CLD[66]. The type, severity of anemia often varies depending on the duration & severity of cirrhosis, presence of complications and possibly the underlying aetiology in many cases. Majority of the cases are either a normochromic normocytic or macrocytic anemia; if associated with haemorrhage then it may be macrocytic.

Multiple mechanisms[67] operate in producing anemia –

- Haemodilution – the plasma volume is frequently increased in patients with cirrhosis, especially with longstanding ascites; this may partly and or even fully account for the low haemoglobin in cirrhosis.
- An important cause of anemia in chronic liver disease is bleeding, especially into the gastrointestinal tract. It may be acute or more often overt chronic bleeding, eventually producing an iron deficiency anemia. The presence of

coagulopathy often enhances the bleeding tendency further contributing to blood loss.

- Nutritional factors play a major role in anemia, patients often being folate deficient. Alcoholics show more nutritional deficiencies than compared to other groups.
- Portal hypertension, splenic sequestration of RBC as a part of hypersplenism.
- The bone marrow response to anemia is reduced as part of chronic disease & increased levels of inflammatory cytokines.
- Other rare causes include aplastic anemia that has been described in Non-A to E hepatitis.
- Sideroblastic anemia that may occur in alcoholics and in hemochromatosis.
- Reduced red cell survival due to multiple mechanisms
- Alcohol is implicated in the pathogenesis of chronic liver disease and contributes to anemia by its direct effects on the liver and by other mechanisms. Eg –direct toxic effects on the erythrocytic precursors in the marrow, folate deficiency etc.

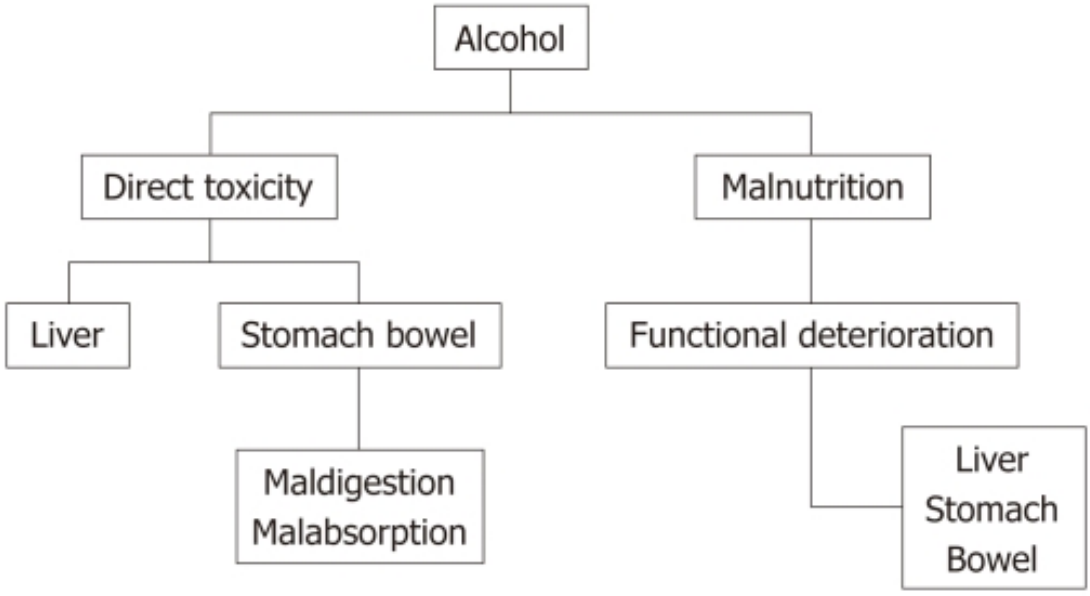


Figure 18: Alcohol and anemia

Iron overload is found to be higher among those who consume more than two alcoholic drinks per day compared to those who don't drink. Cases of sideroblastic anemia complicating alcoholic liver disease have been reported. Alcoholics tend to be more deficient in folate due to the antifolate actions of alcohol.

RBC SURVIVAL & HAEMOLYTIC ANEMIA[68]

Increased red cell destruction is almost constant in chronic liver disease and liver cell failure. Subiyah and Al-Hindawi using radiolabelled red cells were able to show decreased red cell survival that co-related well with splenomegaly and portal hypertension. The mechanisms are multifactorial -

The major factor is hypersplenism with destruction of red cells in the spleen. Spur cells commonly found in chronic liver disease have membrane defects, particularly decreased fluidity and this with altered architecture exacerbates splenic destruction. Coombs negative hemolytic anemia may occur in Wilson's disease due to the toxic effects of free copper on RBC membrane. Rarely a Coombs positive

hemolytic anemia is seen chronic hepatitis, primary biliary cirrhosis & primary sclerosing cholangitis.

A rare syndrome of haemolysis with hyperlipidemia and acanthocytes has been described in patients with chronic alcoholic liver disease (Zieves syndrome). Instability of Pyruvate Kinase enzyme in alcoholic chronic liver disease contributes to haemolysis.

Table 6: ANEMIA IN DCLD[69]

ANEMIA IN CHRONIC LIVER DISEASE
Anemia of chronic disease
Folate deficiency
Iron deficiency (blood loss)
Aplastic anaemia (viral hepatitis, rare)
Sideroblastic (alcohol)
Hypersplenism
Microangiopathy/disseminated intravascular coagulation (DIC) (Rare)
Autoimmune (rare)

LIVER DISEASE & HEMATINIC METABOLISM

IRON METABOLISM

Iron status is largely influenced by the severity of chronic liver disease, complications like upper GI bleed and the use of alcohol.

In uncomplicated cirrhosis the usual pattern is a low normal serum iron levels with normal Total iron binding capacity. TIBC is a function of the amount Transferrin available in he blood. Transferrin is a Beta Globulin synthesized by the liver and hence in advanced liver disease where synthetic capacity is reduced, transferrin levels & hence TIBC is reduced.

Hepatic inflammation and necrosis tends to increase Ferritin levels both due to loss of storage capacity as well as an acute phase response. Large amounts of pro-inflammatory cytokines are produced, especially IL-6 that up regulates Hepcidin levels in the intestine and other cells. Hepcidin down regulates Ferroportin and reduced iron absorption from the intestines, hence producing a combination of high serum Ferritin levels coupled with low serum Iron and low normal Transferrin levels. This exemplifies the anemia of chronic disease, the most common type of anemia in chronic liver disease.

Patients who present with chronic upper GI bleed often develop Iron deficiency anemia characterized by low Ferritin, low serum iron and increased TIBC due to elevated Transferrin levels. However chronic liver disease acts as a confounding factor in terms of Ferritin levels and Transferrin levels; moreover the rise in MCV, which accompanies CLD and alcohol ingestion, may mask iron deficiency. All proliferating cells express membrane transferrin receptors[70] to acquire iron; a small amount of this receptor is shed into blood, where it can be detected in free soluble form. At times of poor iron stores, cells up-regulate transferrin receptor

expression and the levels of soluble transferrin receptor increase. This can be used to distinguish storage iron depletion in the presence of acute phase response or liver disease when a raised level indicates iron deficiency.

Alcoholic liver disease (ALD) is associated with iron overload[71]. The exact mechanism is not known but 2 theories have been proposed – alcohol induces expression of transferrin receptor 1 in intestinal cells thereby enhancing iron absorption and also down-regulates hepcidin thereby up-regulating ferriportin and enhancing iron absorption.

VITAMIN B12 & FOLATE METABOLISM[72]

The liver stores folic acid & converts it to its active storage form tetrahydrofolate. Chronic liver disease is usually accompanied by folate deficiency especially alcoholic liver disease. This is largely due to dietary deficiency. Serum folate levels are almost always low.

The liver stores about 2 to 4 mg of Vitamin B12. Hepatic levels are reduced in liver disease. When hepatocytes become necrotic the vitamin is released into the blood and high serum B12 levels are recorded.

Altered B12 and folate metabolism causes macrocytosis.

CHANGES IN RED CELL SHAPE

Wide variety of changes in the red cell shape[73] may be seen.

1. MACROCYTES

Macrocytosis is commonly seen chronic liver disease per se & especially pronounced in alcoholic liver disease. The increase in MCV is due to:

- there is loading of the RBC membrane with cholesterol & lecithin due to the inhibition of Lecithin Cholesterol Acyl Transferase by the accumulating bile acids.
- Deficiency of folic acid & abnormalities of B12 metabolism
- Reticulocytosis associated with haemolysis and haemorrhage
- Intrinsic abnormalities of bone marrow function

2. MICROCYTIC HYPOCHROMIC CELLS

Red cells are often microcytic hypochromic due to chronic gastrointestinal bleeding, leading to iron deficiency. In portal hypertension, anaemia follows gastro-esophageal bleeding and is enhanced by thrombocytopenia & disturbed blood coagulation. These patients also have increased incidence of acid peptic disease & ulcer bleed that contributes to bleeding.

3. NORMOCYTIC CELLS

This is a combination of macrocytosis of chronic blood loss and the macrocytosis inherent with chronic liver disease.

4. TARGET CELLS

They are also called thin macrocytes, found in both hepatocellular & cholestatic jaundice. Alcoholics show genuine thick macrocytes related to the toxic effect of alcohol on the bone marrow.

5. SPUR CELLS / ACANTHOCYTES

They are cells with unusual thorny projections. Usually associated with far advanced liver disease especially alcoholic liver disease. Their appearance is a bad prognostic sign.

Bone marrow of chronic hepatocellular failure is hyperplastic and normoblastic. In spite of this, erythrocyte volume is depressed and the marrow therefore does not seem able to compensate completely for the anaemia (Relative Bone Marrow Failure)

Table 7: ABNORMALITIES OF RBC SHAPE IN CLD[74]: COURTESY OXFORD TEXTBOOK OF HEPATOLOGY

ABNORMALITY	PRIMARY LIVER DISEASE	DISEASE IN OTHER SYSTEMS
MACROCYTES	MANY LIVER DISEASES	MEGALOBLASTIC ANEMIA HYPOTHYROIDISM CYTOTOXIC DRUGS
TARGET CELLS	MANY LIVER DISEASES	THALASSAEMIA HYPOSPLENISM OTHER HAEMAGLOBINOPATHIES
SPHEROCYTES	ZIEVES SYNDROME	HEREDITARY SPHEROCYTOSIS AUTOIMMUNE HEMOLYSIS BURNS
ACANTHOCYTES	SEVERE CHRONIC LIVER DISEASE	ABETALIPOPROTENEMIA
SCHISTOCYTES	HEPATORENAL SYNDROME	DIC, TTP, HUS, HITT SYNDROME, MALIGNANT HYPERTENSION
STOMATOCYTES	ALCOHOLIC CIRRHOSIS	HEREDITARY STOMATOCYTOSIS

WBC CHANGES IN CHRONIC LIVER DISEASE

WBC abnormalities in chronic liver disease may be due to underlying disease or complications like infection. Leucocytosis can occur in response to infection, haemorrhage, alcoholic hepatitis, cholangitis, hepatic abscess and malignancy.

Leucopenia is usually in the order of $1.5 – 3.0 * 10^9$ cells with predominant depression of polymorphs. It may be due to hypersplenism, toxic effects of alcohol on the marrow or even ineffective haematopoiesis accompanying folate deficiency. Very little is known about the role of granulocyte colony-stimulating factor (G-CSF) or granulocyte macrophage colony-stimulating factor (GM-CSF) in leucopenia associated with cirrhosis[75]. Gurakar et al have shown that GM-CSF treatment for seven days in patients with cirrhosis and leucopenia resulted in an increase in the WBC count. Moreover, they showed no increase in the fraction of trapped leukocytes in the spleen.

Neutrophil function is also affected. A study by Altin et al demonstrated abnormal Neutrophil adhesion and chemotaxis in patients with decompensated chronic liver disease. There are low levels of serum complement C3.

Hypergammaglobulinemia is almost universal in chronic liver disease. It is due to immunization of the antigen presenting cells with enteric microbes and antigens that bypasses the filtering function of the liver via portosystemic shunts. IgA is markedly elevated in alcoholic cirrhosis whereas IgG is markedly elevated autoimmune hepatitis.

PLATELET ABNORMALITIES IN CHRONIC LIVER DISEASE

Abnormalities in platelet count and function are common in patients with all forms of liver disease.

PLATELET COUNT

The thrombocytopenia of chronic liver disease[76] (60 to 90 * 10^9) is very common due to multiple factors.

- Splenic sequestration
- Low levels of Thrombopoietin
- Reduced half-life possibly related to auto-antibodies
- Hypersplenism
- Folate deficiency
- Alcohol induced bone marrow suppression
- Low grade DIC

PLATELET FUNCTION

There is growing evidence of impaired platelet function in chronic liver disease. In particular aggregation[77] is impaired in patients with advanced cirrhosis. This may be due to -

- There is reduced availability of arachidonic acid for the synthesis for prostaglandins and also a reduction in platelet ATP and 5 HT.
- Cross incubation studies suggest the possibility of a circulating factor that inhibits platelet aggregation
- HDL isolated from patients with cirrhosis inhibited ADP induced platelet aggregation.
- It is also reported that basal cytosolic content of calcium in platelets from cirrhosis was lower than of control.

- Even though VWB factor levels were relatively high in patients with cirrhosis, platelet-binding domains were defective contributing to defective adhesion.
- High levels of platelet immunoglobulin's were detected particularly in primary biliary cirrhosis, alcoholic cirrhosis and chronic active hepatitis.

The measurement of bleeding time assess the contribution of platelet number and function to primary haemostasis but does not have a close relationship to bleeding time, contrary to that found in patients with bone marrow diseases like leukaemia.

HAEMOSTASIS IN CHRONIC LIVER DISEASE

The liver plays a central role in haemostasis and thrombosis. Liver parenchymal cells are the site of synthesis of most coagulation factors, the physiologic inhibitors of coagulation- protein C, protein S, and Antithrombin, and essential components of the fibrinolytic system- plasminogen, $Alpha_2$-antiplasmin, and thrombin activatable fibrinolysis inhibitor (TAFI)[78].

The liver also regulates haemostasis and fibrinolysis by clearing activated coagulation factors and enzyme-inhibitor complexes from the circulation. Therefore, when liver dysfunction occurs in patients with liver disease, a complicated haemostatic derangement ensues, which can lead to bleeding, thrombosis, or neither bleeding nor thrombosis.

Table 8: Effects of liver disease on haemostasis[79]

HAEMOSTASIS IN LIVER DISEASE
1. Reduced synthesis of clotting factors -Hepatic dysfunction per se - Vitamin K deficiency
2. Reduced synthesis of endogenous anticoagulants
3. Production of abnormal dysfunctional proteins
4. Enhanced Fibrinolytic activity - Reduced clearance of activators of Fibrinolysis - Reduced production of inhibitors of fibrinolysis
5. Reduced Hepatic clearance of activated clotting factors
6. Disseminated Intravascular Coagulation
7. Platelet abnormalities

REDUCED SYNTHESIS OF CLOTTING FACTORS

The liver is the site of synthesis of most procoagulant proteins. As a result, decreased levels of coagulation factors V, VII, IX, X, and XI and prothrombin are commonly observed in patients with liver failure.[80] In contrast, factor VIII levels are increased which may be related to the elevated level of its carrier protein VWF and to decreased clearance of factor VIII from the circulation by the liver low-density lipoprotein-related receptor.[81] Factor VIII is synthesized primarily in hepatic sinusoidal endothelial cells, whose function is preserved in liver disease. Qualitative

defects in clotting factors can arise as a consequence of hepatic failure. Because of vitamin K deficiency or decreased production of gamma glutamic carboxylase, a proportion of circulating vitamin K dependent coagulation factors II, VII, IX, and X may be deficient in -carboxylated glutamic acid residues giving rise to impaired function of these factors.

REDUCED SYNTHESIS OF ENDOGENOUS ANTICOAGULANTS

Levels of anticoagulant protein C, protein S, anti-thrombin, heparin cofactor II, and $Alpha_2$-macroglobulin are decreased in patients with liver disease. Because tissue factor pathway inhibitor (TFPI) is mainly synthesized by endothelial cells, normal levels of this protein are present in patients with hepatic failure.

PRODUCTION OF DYSFUNCTIONAL PROTEINS

DYSFIBRINOGENEMIA

Fibrinogen levels are in the normal range in patients with chronic liver disease, but may be decreased in patients with decompensated cirrhosis. The dysfibrinogen is characterized by an increased content of sialic acid,[82] possibly caused by enhanced levels of glycosyltransferases in hepatocytes. Hypersialization of fibrinogen impairs its polymerization but does not affect the interaction of fibrinogen with platelets.

Dysfibrinogenemia accounts for the prolonged thrombin time in patients with chronic liver disease. This should be suspected when aPTT is prolonged with normal fibrinogen levels and fibrinogen degradation products within the normal range.

Von Willi Brand Factor

Profoundly elevated levels of von Willebrand factor (VWF) antigen are frequently observed in patients with liver disease and were suggested to result from endothelial damage possibly mediated by bacterial infection. The high levels of VWF

may ameliorate the hemostatic defect caused by thrombocytopenia and platelet function defects.[83] In patients with liver disease the regulation of VWF multimer size and activity can be impaired because of reduced synthesis of VWF-cleaving protease ADAMTS13 (a disintegrin-like and metalloprotease with thrombospondin type 1 repeats) by stellate cells in the liver.[18] However, a reduced multimer size of VWF was found in patients with liver disease, suggesting that other proteases, such as plasmin, elastase, and granzyme B, contribute to VWF proteolysis.

ENHANCED FIBRINOLYTIC ACTIVITY

There is evidence for enhanced fibrinolytic activity in patients with liver disease. Hepatocytes synthesize plasmin inhibitors such as $Alpha_2$ anti-plasmin as well as tissue plasminogen activator inhibitor (PAI).

In patients with cirrhosis PAI is reduced even without features of clotting activation. The clearance of Tissue plasminogen activator by the hepatocytes is decreased. The resultant increase in the ratio of plasminogen activator to its inhibitor is thought to lead to enhanced fibrinolysis.Ascitic fluid contains plasminogen activators as well as fibrin degradation products indicating active intraperitoneal coagulation. This accounts for the increased bleeding tendency following LeVeen shunt.

DISSEMINATED INTRAVASCULAR COAGULATION

The release of tissue thromboplastin like material by necrotic liver coupled with low-grade endotoxemia & reduced clearance of activated clotting factors contributes to the triggering of DIC in patients with severe chronic liver disease. Whatever the background state, cirrhotic patients are at a greater risk of DIC particularly when complicated by sepsis and hypotension.

CONCEPT OF REBALANCED HAEMOSTATIC SYSTEM

Because both procoagulant and anticoagulant proteins decline in patients with liver diseases, it appears that the hemostatic system is rebalanced. This may explain why most patients with liver disease usually do not exhibit severe bleeding manifestations during invasive procedures, and why patients are not protected against thrombosis.This balance is quite delicate and vulnerable to be tipped toward bleeding or thrombosis depending on the particular trigger that is inflicted.

IMPAIRED HAEMOSTASIS	CHANGES THAT PROMOTE HAEMOSTASIS
Thrombocytopenia	Elevated levels of VWF
Platelet function defects	Decreased levels of ADAMTS-13
Low levels of factors II, V, VII, IX, X, and XI	Elevated levels of factor VIII
Vitamin K deficiency	Decreased levels of protein C, protein S, antithrombin, alpha$_2$-macroglobulin, and heparin cofactor II
Dysfibrinogenemia	
Elevated t-PA levels	Low levels of plasminogen
Low levels of $_2$-antiplasmin, factor XIII, and TAFI	

Table 9: REBALANCED HEMOSTATIC SYSTEM[84]

DESIGN OF THE STUDY

MATERIALS AND METHODS

To assess the hematological abnormalities in decompensated chronic liver disease, a cross sectional analytical study was conducted in Tirunelveli Medical College hospital from June 2011 to September 2012.

50 patients admitted to the General Medical and Intensive Medical care unit with clinical features suggestive of decompensated chronic liver disease were taken up for the study.

Patients suffering from acute liver cell failure, known GI malignancy or known primary hepatocellular carcinoma, primary coagulation disorders , liver cell failure due to infective causes, from end stage medical diseases like COPD, Coronary artery disease, cardiac failure, CKD were excluded from the study.

All patients taken up for the study were evaluated in detail. Oral consent was obtained for clinical examination and lab investigations. Written consent was obtained for procedures such paracentesis, Upper GI endoscopy and viral marker studies.

Following points were noted in history

- Fatigue and weight loss
- Anorexia and flatulent dyspepsia
- Abdominal pain
- Jaundice, itching, colour of urine and feces
- Swelling of legs and abdomen
- Haemorrhage – haemetemsis, malaena, nose, gums, skin
- Loss of libido; menstrual history

- Urine output
- Past history : jaundice, hepatitis, drugs ingested, blood transfusions, diabetes, hypertension, tuberculosis, coronary artery disease, trauma, surgeries, needle prick injuries
- Personal history – Alcoholism, smoking, high risk behaviour
- Family history – liver disease, autoimmune disease

A detailed clinical examination was done in all cases

- Nutrition, fever, fetor hepaticus, jaundice, pigmentation, purpura, clubbing, white nails, vascular spiders, palmar erythema, gynecomastia, testicular atrophy, distribution of body hair, parotid enlargement , dupytrens contractures, vital signs.
- Abdomen – ascites, abdominal wall veins, liver , spleen , bruits
- Neurological changes – mental functions, flapping tremor and constructional apraxia

Patients were submitted to a number of blood investigations; samples obtained were personally handed over to the lab and results were obtained in person. Blood samples were anticoagulated when needed with EDTA.

Clinical examination and basic investigations help in establishing a diagnosis of chronic liver disease. According to Schiff Hepatology 11th edition chapter 1 page 3 line 3 - The presence of two physical findings (ascites and evidence of portosystemic encephalopathy (asterixis) and two laboratory findings (hypoalbuminemia (<2.8 g/dL) and a prolonged prothrombin time (international normalized ratio >1.6) indicates a diagnosis of cirrhosis of the liver.

Clinical findings are supported by USG evidence of cirrhosis, which can detect 95 % of cirrhosis (Schalm Sw. The diagnosis of cirrhosis J.Hepatol 1997; 27:1118)

After establishing the diagnosis, patients were evaluated for hematological abnormalities. All investigations were done at the clinical pathology lab at Tirunelveli Medical college hospital except Iron studies, folate, B12 and fibrinogen levels which were done at an outside lab due to unavailability at the medical college laboratory.

RBC abnormalities

1. RBC Count – RBC count are done in Neubauers chamber using Hayems fluid or autoanalyser.

   Normal value – 4.5 to 6 million per mm^3

2. Hemoglobin estimation - done by Sahlis method, based on conversion of hemoglobin to acid hematin or auto analyzer.

   Normal value – Male – 14 to 18 gm %, females – 12 to 16 g %

3. Packed cell volume (PCV): It is done in autoanalyser or using microhematocrit capillary method.

   Normal value : Male 42 to 52%. Female: 37 to 47 %

4. MCV, MCHC, MCH:

   - are estimated by autoanalyser

   MCV - 80 to 97 fl

   MCH - 26 to 33 pg/dl

   MCHC - 32-35 gm/dl.

5. Peripheral smear for blood picture

Using stains, blood picture is examined with a standard lab microscope.

Low power field examination:

Quality of film

Number, distribution and staining of WBCs

RBCs examination

High power field examination:

Assess RBC – Size, Shape,Hemoglobin concentration

Oil immersion examination:

Assess atypical cells and inclusion bodies

6. Reticulocyte count:

Stain - 1% brilliant cresyl blue

Normal - 0.2-2%

To assess WBC abnormality:

1. Total WBC count: Done by QBC method or using Neubauer's chamber with Turke's fluid

Normal 3,800-9,000 cells per mm3

2. Differential count: Assessed by QBC method or direct staining and visualizing with lab microscope.

To Assess hemostasis

1. Platelet count : estimated by autoanalyser, if found to be low, collaborated with peripheral smear; if discrepancy between platelet count and peripheral smear then a manual count was done manually by Rees-Eecker method i.e with staining with brilliant cresyl blue dye.
2. Prothrombin time: Normal 10-14 sec.

3. Activated partial thromboplastin time: Normal 24-34 sec.

4. Fibrinogen levels

Reference range – 150 to 400 mg/dL

Iron Studies (chemiluminescent method)

- Serum iron (50 to 170ug/dL)
- Ferritin levels (10 to 291 ng/ml)
- Iron binding capacity (250 to 450 ug/dL)
- Transferrin (176 to 280 ug/dL)
- Transferrin saturation (20 to 50%)

Folate levels (> 5.38 ng/ml) (chemiluminescent method)

B12 levels (118 to 800 pg/ml) (chemiluminescent method)

Upper GI endoscopy

UGI endoscopy was done at medical gastroenterology department. After obtaining the patient's written informed consent, Patients were kept on over night nil oral and upper GI endoscopy was done. Results were collected in person and were correlated with other findings to establish the diagnosis.

INCLUSION CRITERIA

1. All patients with liver disease whose symptoms and signs persists for more than 6 months

2. Alcoholic cirrhosis, post-necrotic cirrhosis, metabolic causes of liver diseases were taken up for the study

EXCLUSION CRITERIA

1. Patients with underlying malignancy or known primary hepatocellular carcinoma were excluded

2. Patients with primary coagulation disorder or primary abnormalities of haemostatic function were excluded.

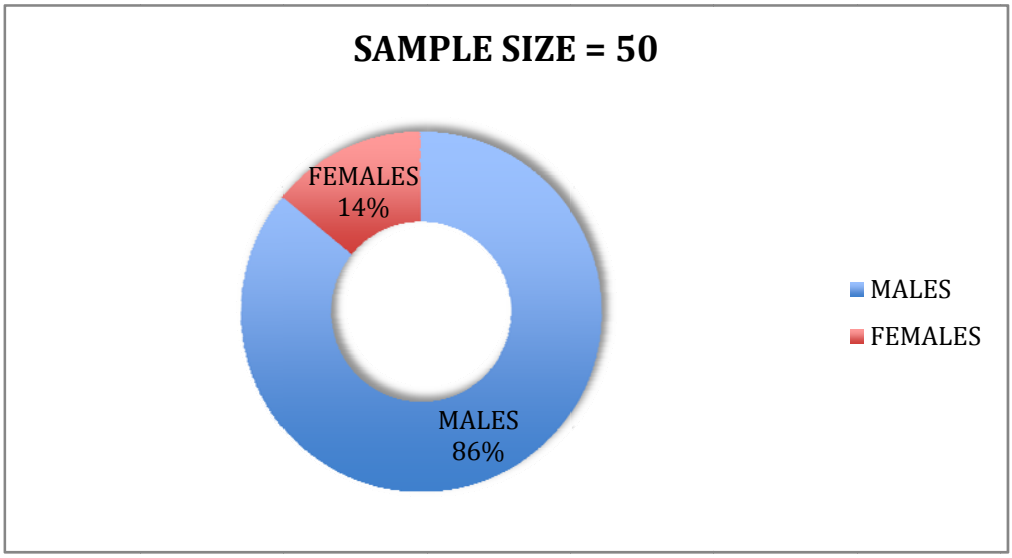
3. Acute hepatic failure was excluded

4.Patients with preexisting anemia due to other causes were excluded.

5. Patients suffering from end stage medical diseases like COPD, Coronary artery disease, cardiac failure, CKD were excluded

OBSERVATION & DATA ANALYSIS

This analytical study to assess the haematological abnormalities in decompensated chronic liver disease was conducted at Tirunelveli Medical College from June 2011 to September 2012.



50 patients with decompensated chronic liver disease admitted to the medical department were taken for the study; this included 43 males (86%) and 7 females (14%).

Table 10: AGE DISTRIBUTION OF CASES

Age	*Males*	*Females*	*Total*	*%*
20 to 30	2	0	2	4
30 to 40	4	3	7	14
40 to 50	16	2	18	36
50 to 60	17	0	17	34
>60	4	2	6	12

The age range was from 24 to 70.The average age of the patients in the study was 48 yrs. 70% of the patients were between 40 and 60 years of age. Only 2 patients were younger than 30 years.

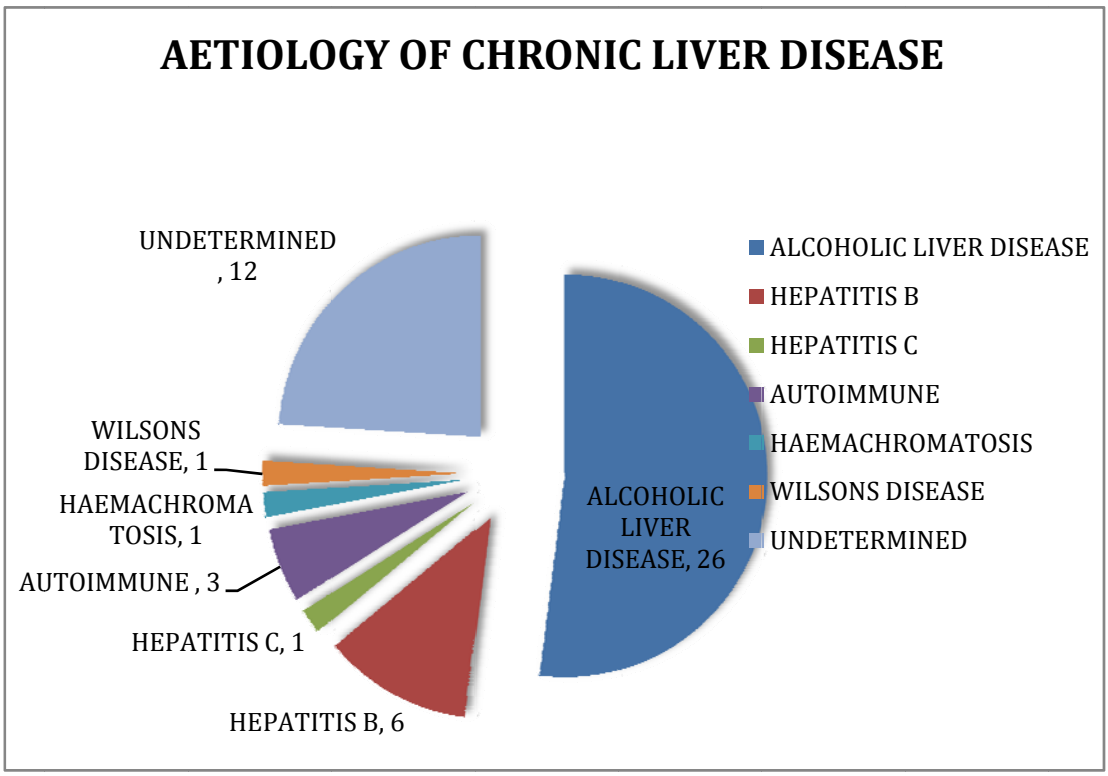


Table 11: AETIOLOGY OF CIRRHOSIS

Aetiology of cirrhosis	*Male*	*Female*	*Total*
Alcoholic liver disease	26	0	26
Hepatitis B	5	1	6
Hepatitis C	1	0	1
Autoimmune	1	2	3
Hemochromatosis	1	0	1
Wilsons disease	0	1	1
Undetermined	9	3	12

52% of the patients had alcoholic cirrhosis all of whom were males. The aetiology of chronic liver disease could not be determined in 24 % of cases but all of them had clinical and radiological features of cirrhosis. Of the 2 young patients (<30yrs) one patient had hemochromatosis & the etiology was unknown in the other.

6 patients had Hepatitis B and 1 had Hepatitis C; all these 7 patients had cirrhosis. Autoimmune hepatitis and cirrhosis were present in 2 females and 1 male patient.

PAST HISTORY OF JAUNDICE

Of the 50 patients with DCLD only 14 patients gave past history of jaundice. Serology proved that 4 patients had hepatitis B and 1 had hepatitis C. One female patient had recurrent history of jaundice and was diagnosed as a case of Wilsons disease.

SERUM PROTEINS

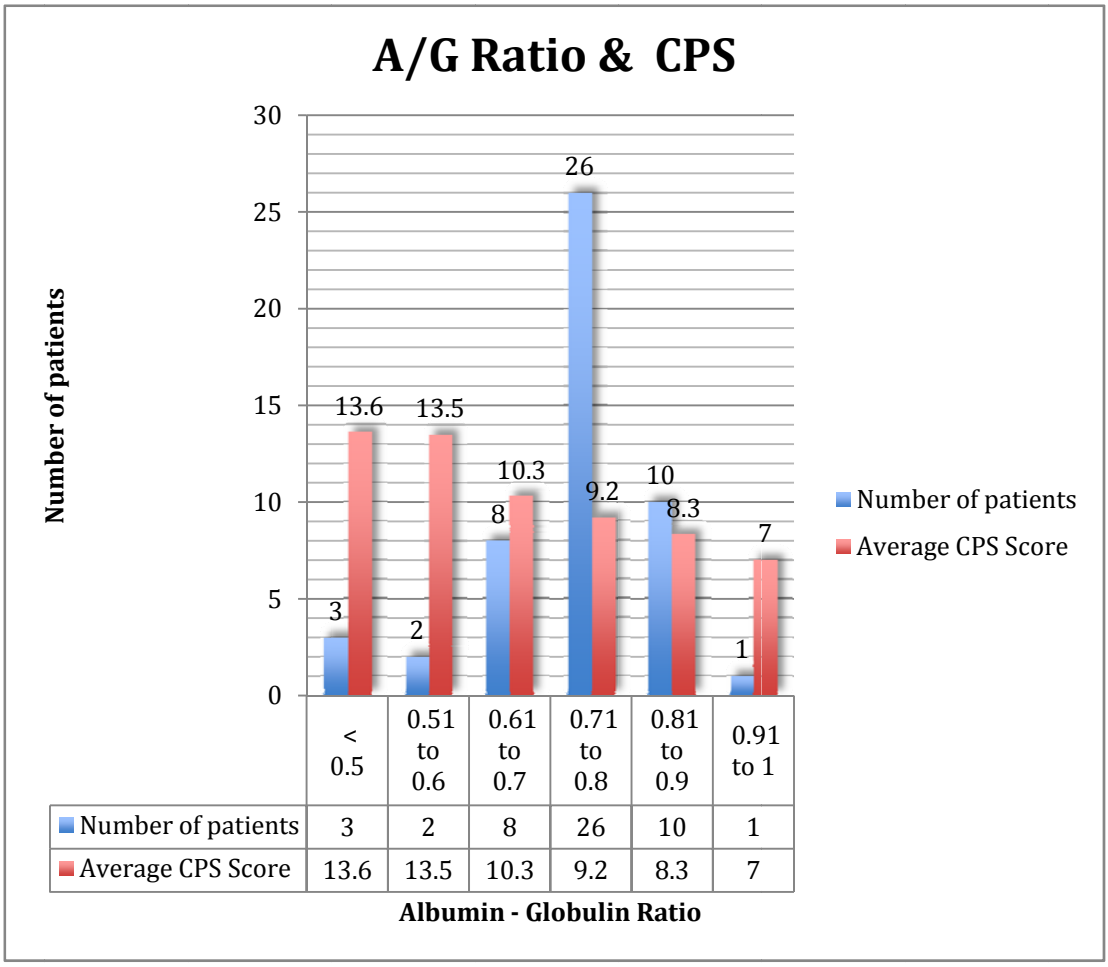
Since one of the major functions of the liver is to synthesize proteins, the total proteins and albumin to globulin ratio was assessed in this study.

Table 12: TOTAL PROTEIN LEVELS

Total protein (A + G)	*Number of Patients*	*%*
< 4	4	8
4 to 5	8	16
5 to 6	30	60
6 to 7	8	16
> 7	0	0

Among 50 patients only 16 % of patients had a total protein level between 6 to 7 g/dL. The rest 84 % had a total protein less than 6 g/dL; majority (60%) falling between 5 to 6 g/dL. 4 patients had a total protein below 4 g/dL. These 4 patients had severe liver disease with an average CPS score of 13; hence reflecting the poor synthetic function of the liver.

Table 13: ALBUMIN-GLOBULIN RATION AND AVERAGE CHILD PUGH SCORE



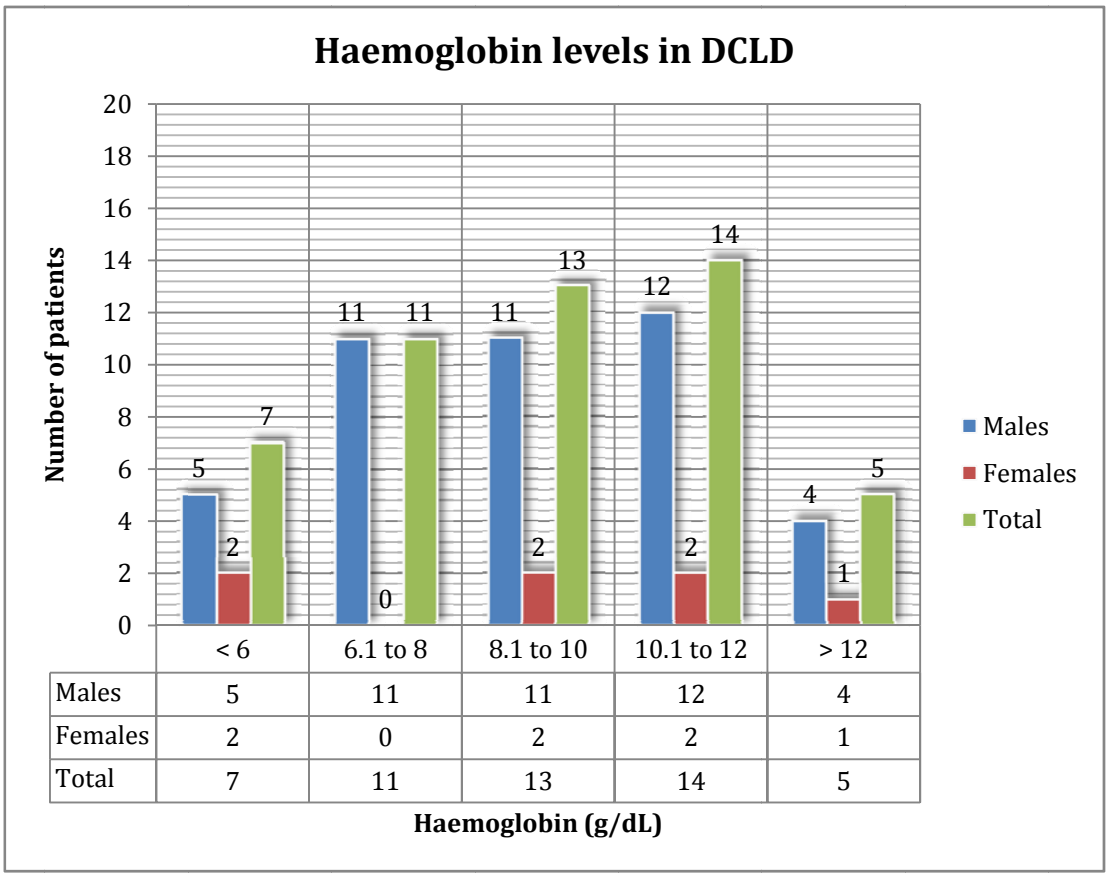
The Albumin to Globulin ratio was reversed in all patients as expected in chronic liver disease. As evident from the above chart, 3 patients had A/G ratio less than 0.5 with an average CPS of 13.6, 2 patients had an A/G ratio in between 0.51 to 0.6 with an average CPS of 13.5, 8 patients had an A/G ratio in between .61 to 0.7 with an average CPS of 10.3, 26 patients had an A/G ratio of 0.71 to 0.8 with an average CPS score of 9.2, 10 patients had an A/G ratio of 0.81 to 0.9 with an average CPS score of 8.3 & only 1 patient had an A/G ratio of .93 with a CPS score of 7.

This clearly shows that lower the A/G ratio more severe the liver disease, as reflected by a higher Child Pugh Score. (P value – 0.03)

ANALYSIS OF RBC

Patients were analyzed for the presence or absence of anemia; & if present the type of anemia was characterized with help of peripheral smear and iron studies.

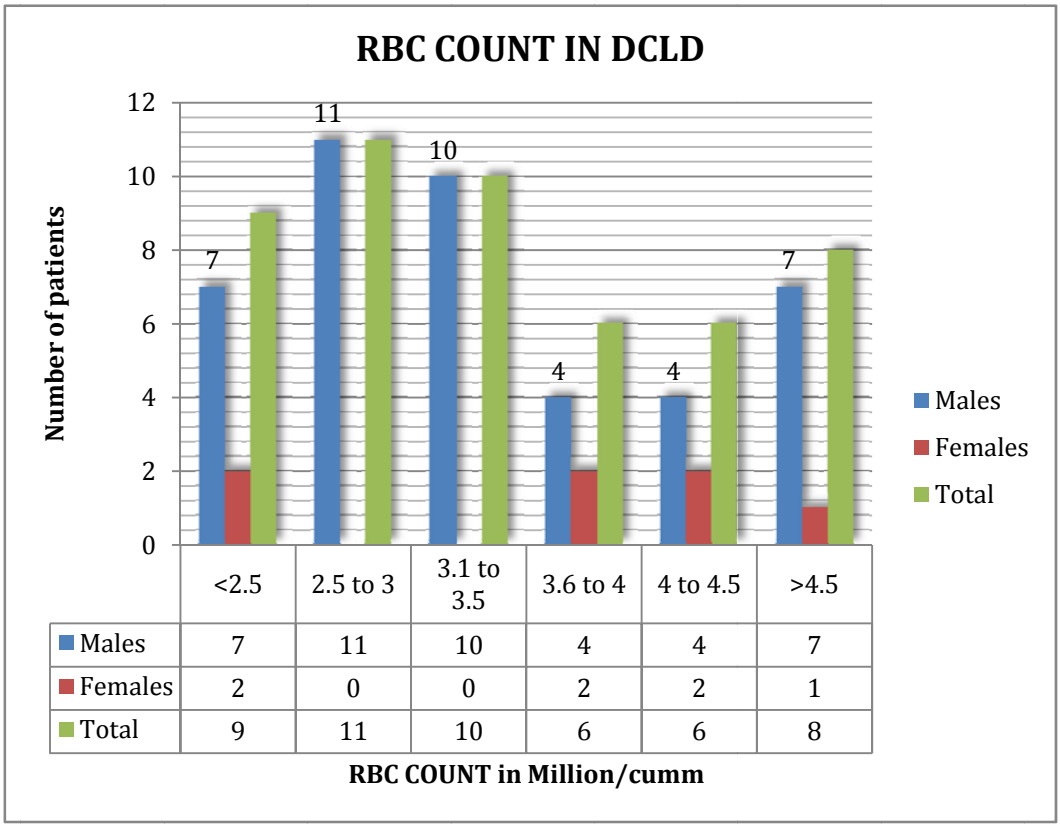
Table 14: HAEMAGLOBIN LEVELS IN DCLD



	< 6	6.1 to 8	8.1 to 10	10.1 to 12	> 12
Males	5	11	11	12	4
Females	2	0	2	2	1
Total	7	11	13	14	5

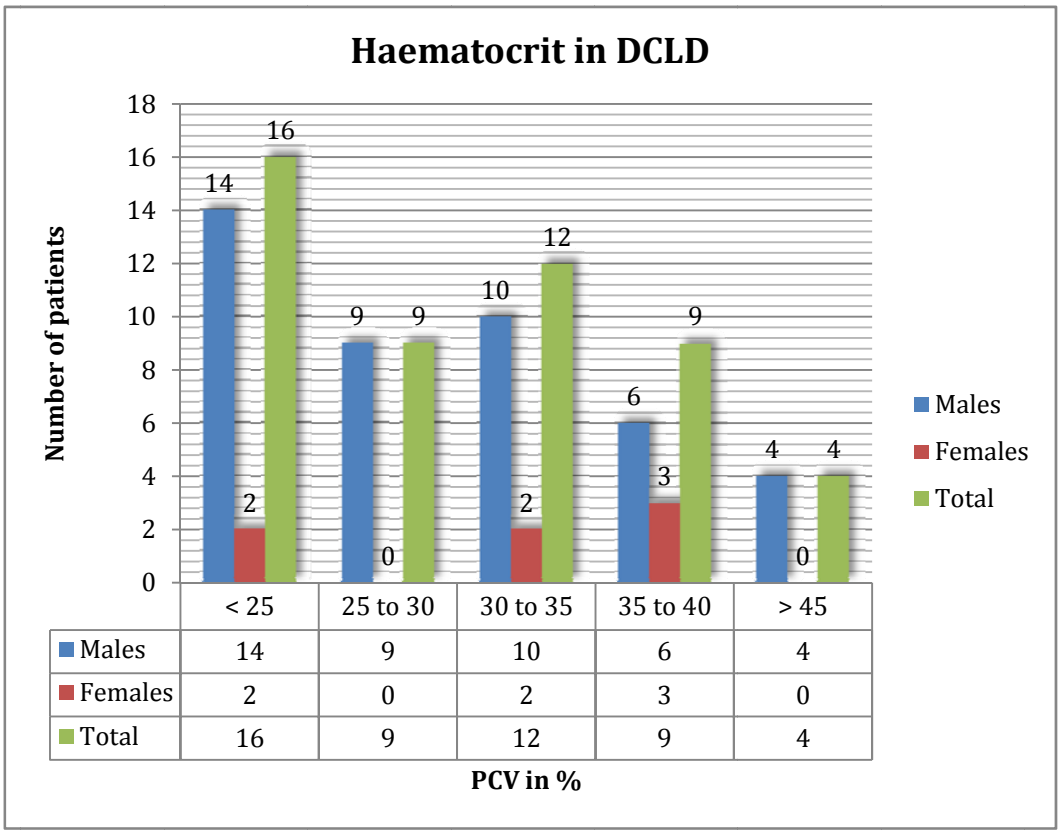
90% of the patients were anemic with only 10% of patients having a normal Hb level above 12 g/dL. About 14 % of patients had severe anemia with an Hb value less than 6 g/dL. All these patients had upper GI bleed.

Table 15: RBC COUNT IN DCLD



	<2.5	2.5 to 3	3.1 to 3.5	3.6 to 4	4 to 4.5	>4.5
Males	7	11	10	4	4	7
Females	2	0	0	2	2	1
Total	9	11	10	6	6	8

Table 16: HAEMATOCRIT IN DCLD



	< 25	25 to 30	30 to 35	35 to 40	> 45
Males	14	9	10	6	4
Females	2	0	2	3	0
Total	16	9	12	9	4

The Hb, RBC count and haematocrit for each individual patient parallels each other, however 16 patients had a haematocrit below 25% (compared to only 7 patients with Hb less than 6g/dL) of which 9 had an upper GI bleed whereas the remaining 7 did not. This can probably be accounted for the haemodilution that accompanies DCLD and was evident at all levels of Hb compared to haematocrit.

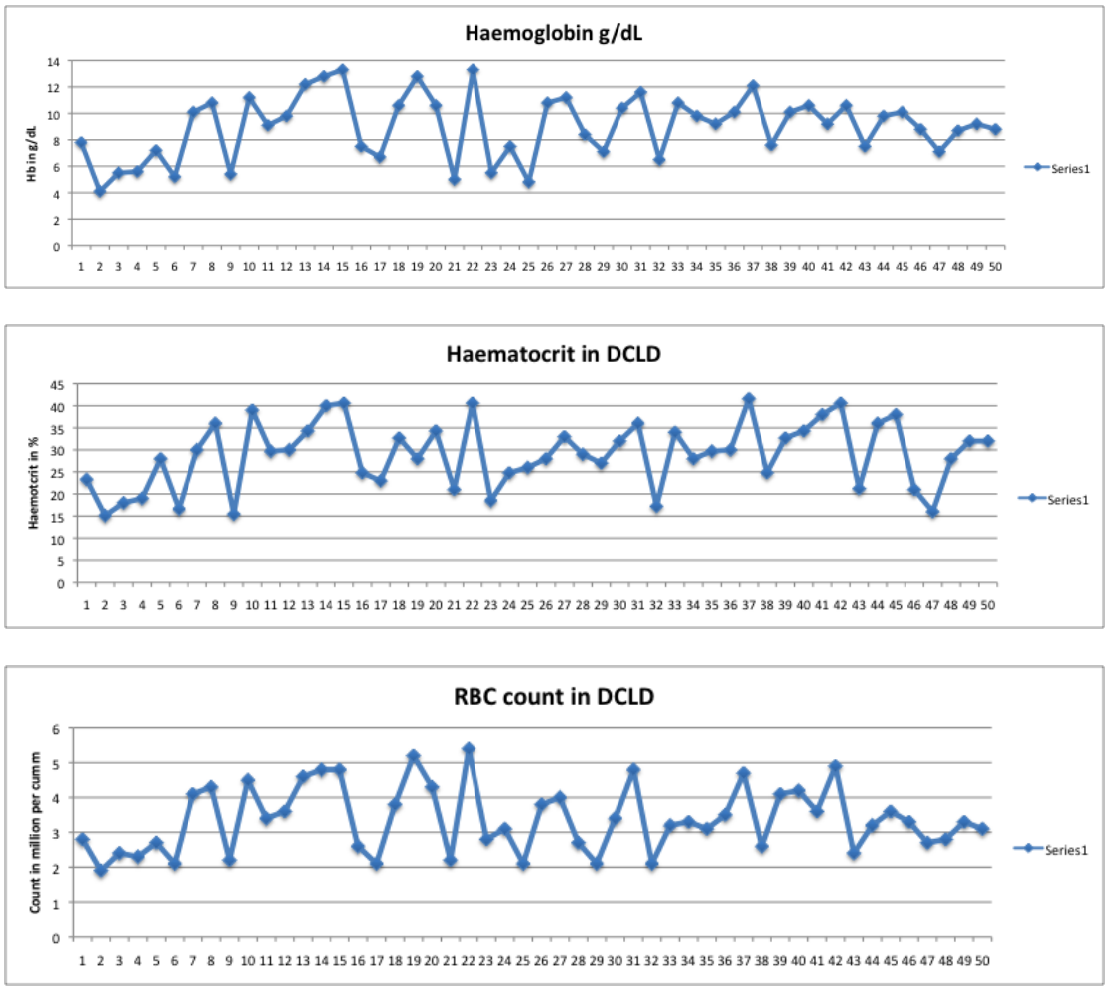
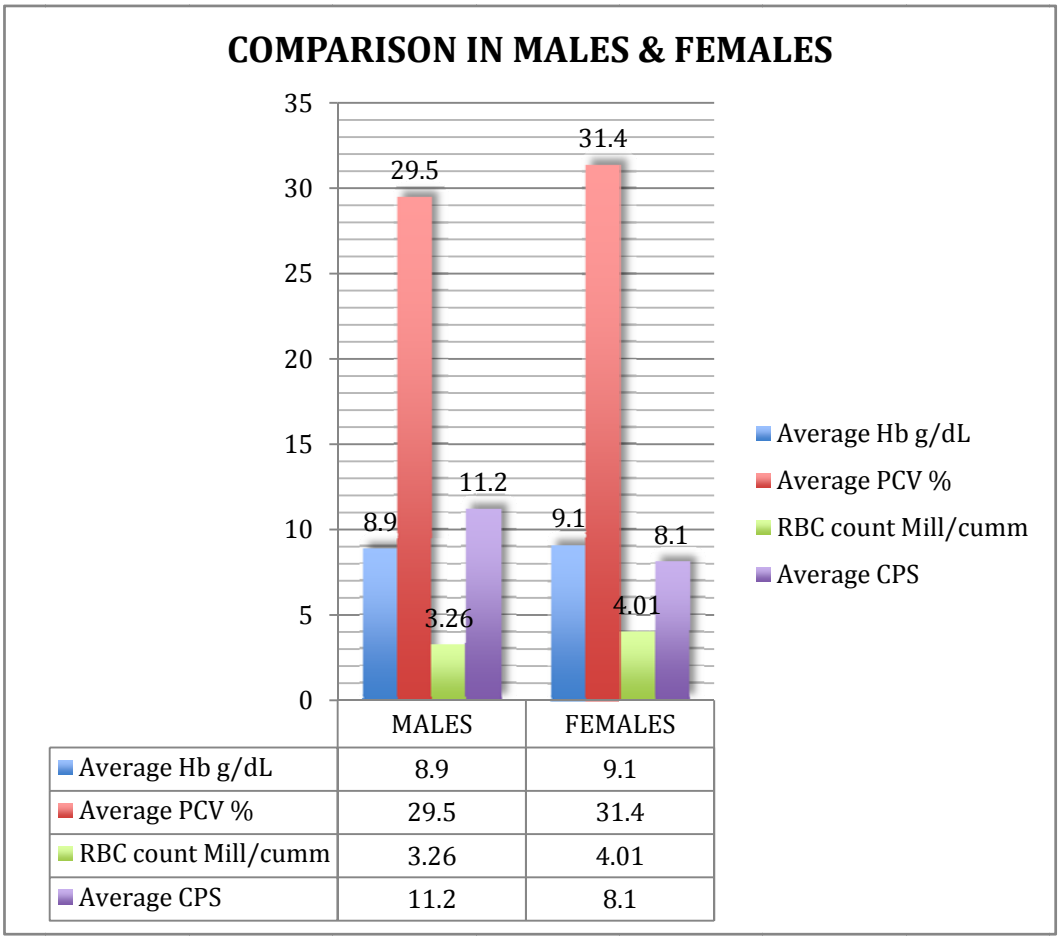


Figure 19; Individual comparison of Hb, PCV & RBC count in each patient

Comparison of the Hb, RBC Count and PCV of males and females were done.

Table 17: Hb, PCV, RBC COUNT IN MALES AND FEMALES



	MALES	FEMALES
Average Hb g/dL	8.9	9.1
Average PCV %	29.5	31.4
RBC count Mill/cumm	3.26	4.01
Average CPS	11.2	8.1

From the above data males had a worse Hb, RBC count & PCV profile compared to females. This can be explained by the following facts

- Males had more severe liver disease compared to females (average CPS of males – 11.2 Vs CPS of females – 8.1)

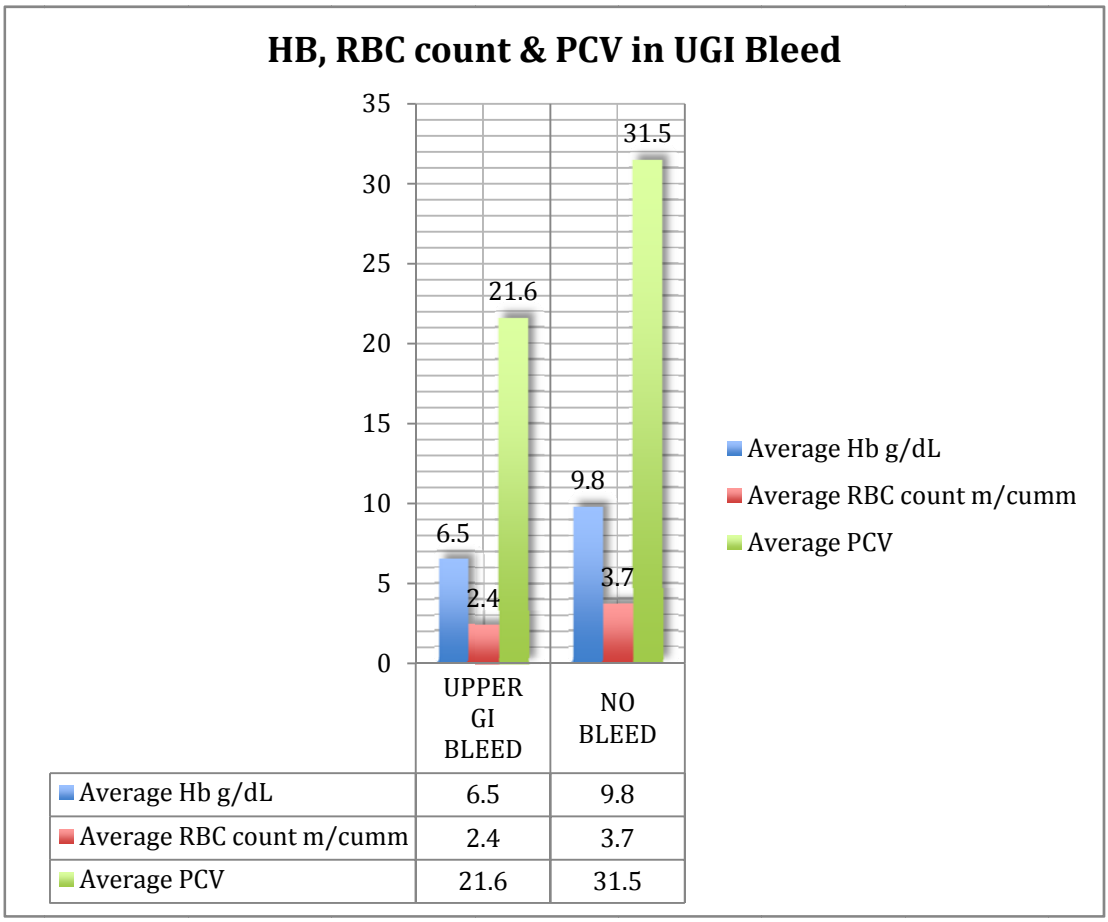
- Eleven males had an upper GI bleed compared to only two females

- 60 % of the males Vs 0 females were alcoholics, which contributes to anemia by various mechanisms like direct toxicity on the bone marrow, direct liver injury, impaired folate absorption and malnutrition etc.

In this study 13 patients had a history or presented with Upper GI bleed. This included 11 males and 2 females. The source of bleed was confirmed to be variceal by

upper GI endoscopy in all 13. The rest 37 patients did not give a history of upper GI bleed and they had a negative stool occult blood test (though 35 patients had evidence of portal hypertension). The average Hb, RBC Count and haematocrit was compared among patient with and without upper GI bleed.

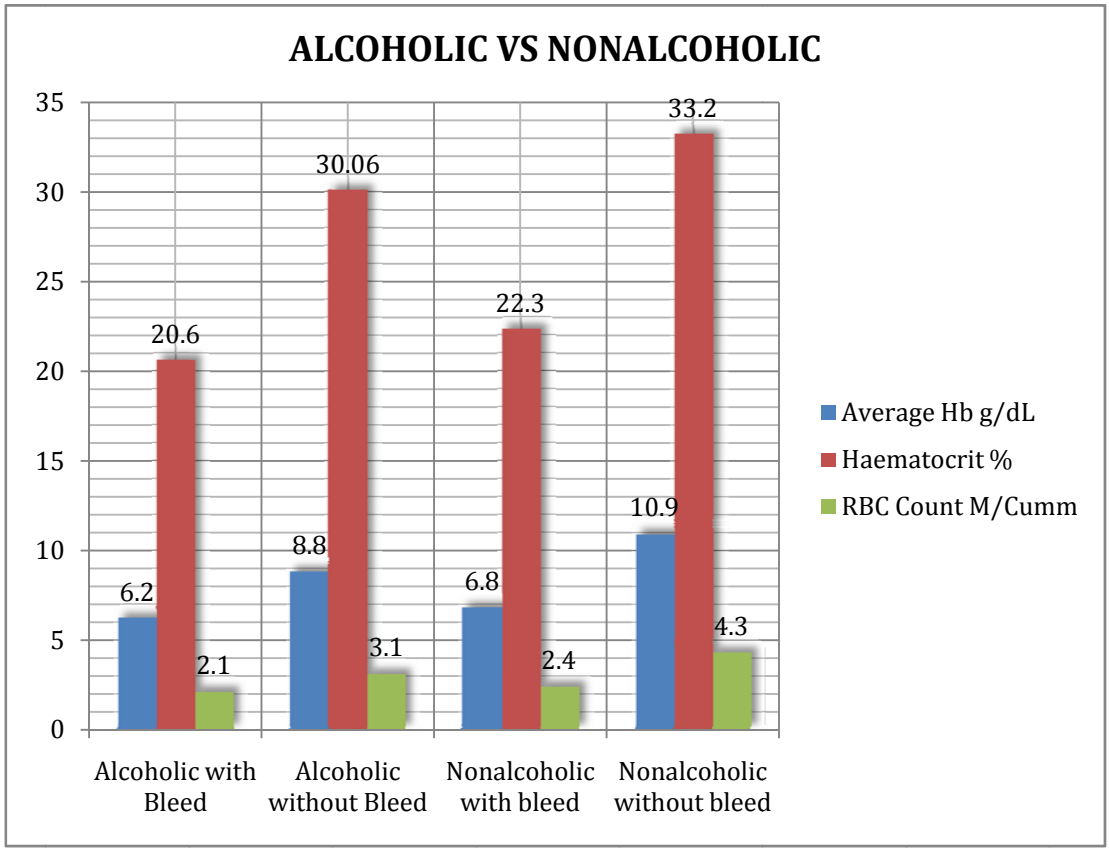
Table 18: COMPARISON OF Hb & PCV IN PATIENTS WITH & WITHOUT UPPER GI BLEED



	UPPER GI BLEED	NO BLEED
Average Hb g/dL	6.5	9.8
Average RBC count m/cumm	2.4	3.7
Average PCV	21.6	31.5

As expected, this data shows a statically significant lower Hb, RBC count and haematocrit in DCLD patients with upper GI bleed compared to patients without bleed. (P value Hb, RBC, PCV - <0.05)The average Hb, RBC Count & PCV were determined and compared among alcoholic and non-alcoholic etiologies of DCLD keeping in mind the presence or absence of upper GI Bleed in each group

Table 19: AVERAGE Hb, PCV, RBC COUNT IN PATIENTS WITH ALCOHOLIC AND NON-ALCOHOLIC LIVER DISEASE WITH OR WITHOUT UPPER GI BLEED



		Average Hb g/dL	*Average PCV %*		*Average RBC M/Cumm*	
Alcoholic Liver disease	With UGI Bleed	6.2	8.7	20.6	27.4	2.1	3.07
	Without UGI Bleed	8.8		30.06		3.1	
Non-alcoholic liver disease	With UGI Bleed	6.8	9.3	22.3	29.5	2.4	3.65
	Without UGI Bleed	10.9		33.2		4.3	

As expected the average Hb, Hct & RBC count in alcoholics as a whole (8.7, 27.4, 3.07), are lower compared to non-alcoholics (9.3, 29.5, 3.07). (P value-<0.05)

Comparing alcoholic and non-alcoholic patients with upper GI Bleed reveals that alcoholic patients with an upper GI bleed have stastically significantly lower values of Hb, PCV and RBC count compared to the latter. (P value -<0.05)

Like wise comparing alcoholic and non-alcoholic patients without any GI bleed also shows stastically significantly lower values among the alcoholic group. (P value –<0.05

CHARACTERISTICS OF THE ANEMIA

The most common type of blood picture was normocytic red cells seen in 22 patients, of which 5 patients had a normal Hb value. Macrocytic picture was observed in 15 patients. Of these 14 patients had alcoholic liver disease and the etiology was undetermined in the other. 11 patients had a microcytic blood picture of which 8 patients had an upper GI bleed and the one patient with hemochromatosis had sideroblastic anemia that was proved with bone marrow and iron studies. Dimorphic blood picture was seen in 2 patients.

Table 20: CHARACTERISTICS & MORPHOLOGY OF ANEMIA

Peripheral smear	*Number*	*Average MCV*
Macrocytic	15	101.8
Normocytic	22	89.9
Microcytic	11	71.39
Dimorphic	2	78

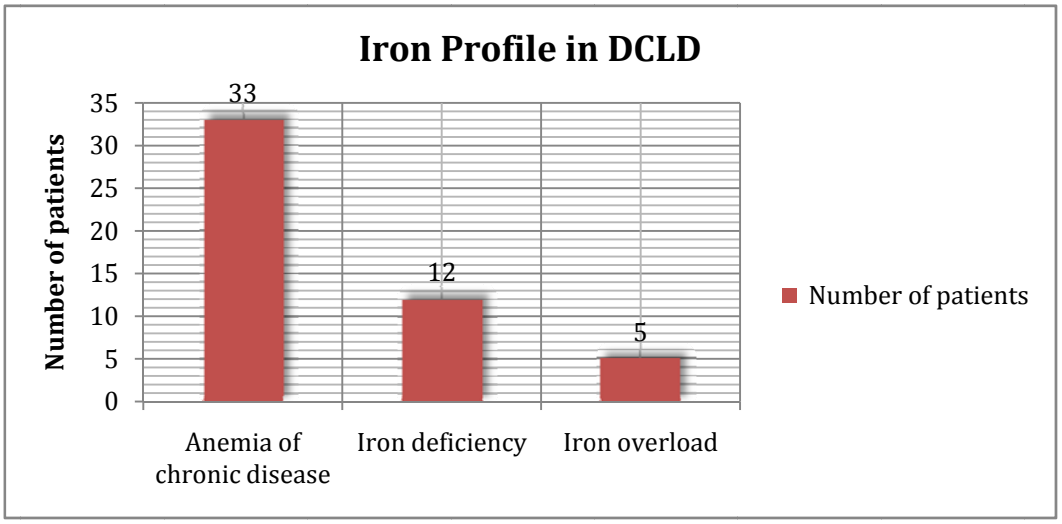
Target cells were seen only in 3 patients and acanthocytes in 2 patients, these patients had severe disease with an average CPS of 13. One female patient with Wilsons disease was noted to have few spherocytes in the peripheral smear. All

patients in this study had a reticulocyte count < 1.2 % suggesting an inadequate marrow response to anemia.

IRON STUDIES

Iron profile was performed for all 50 patients in this study group in order to correlate with the Hb values and determine the type of anemia. Moreover Ferritin is produced and stored in the liver, so is Transferrin. Hence changes in the values of these parameters in relation to the severity of DCLD were also determined.

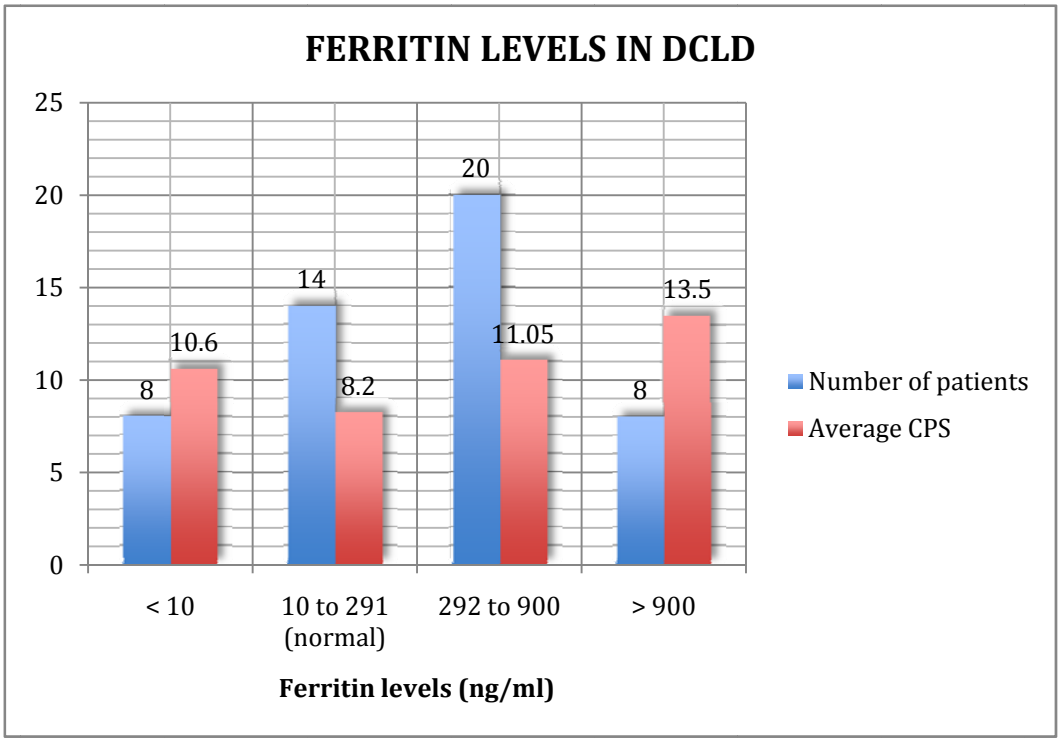
Table 21: IRON PROFILE IN DCLD



Anemia of chronic disease was the most common type noted in 33 patients. 12 patients had iron deficiency of which 11 patients had Upper GI bleed. Iron overload pattern was noted in 5 patients, 4 of these patients had alcoholic liver disease and one patient had hemochromatosis.

Ferritin is a protein-iron complex that is found in highest levels in the liver, spleen and bone marrow. The levels of ferritin were determined in all 50 patients as a part of the iron profile and compared to the Child Pugh Score.

Table 22: FERRITIN LEVELS IN DCLD

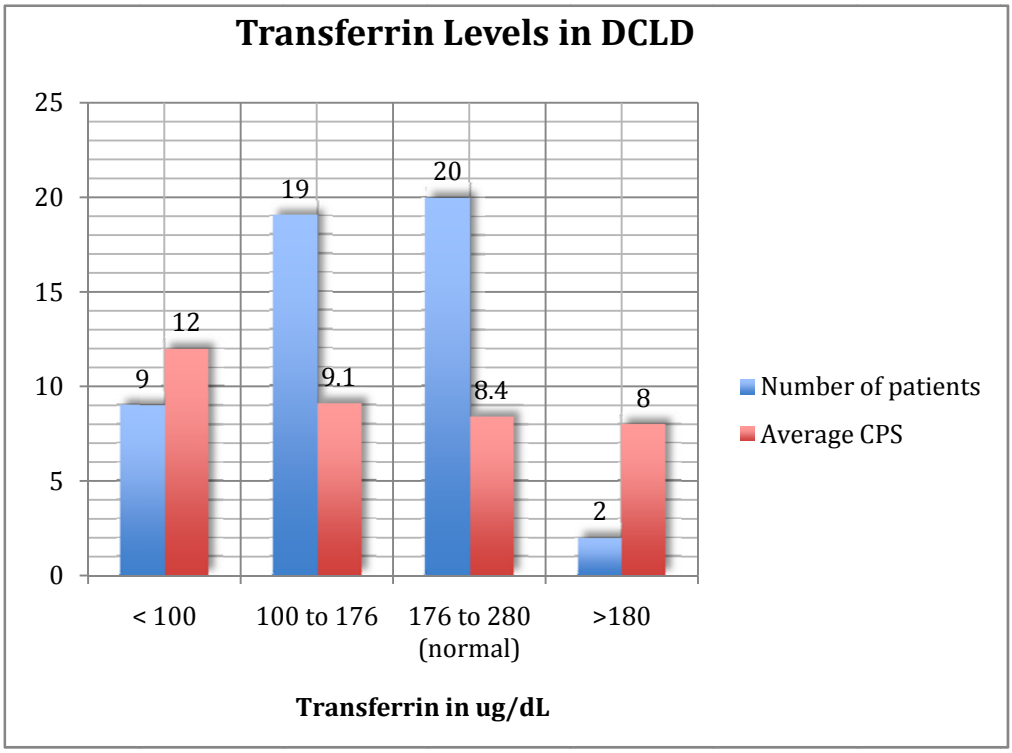


14 patients had a normal level of Ferritin and their average CPS was 8.2. As the level of ferritin rises the average CPS also rises reflecting increasing severity of disease (p value - .007). This is probably because with increasing damage to liver cells the ability to store ferritin is lost which leaks out into circulation.

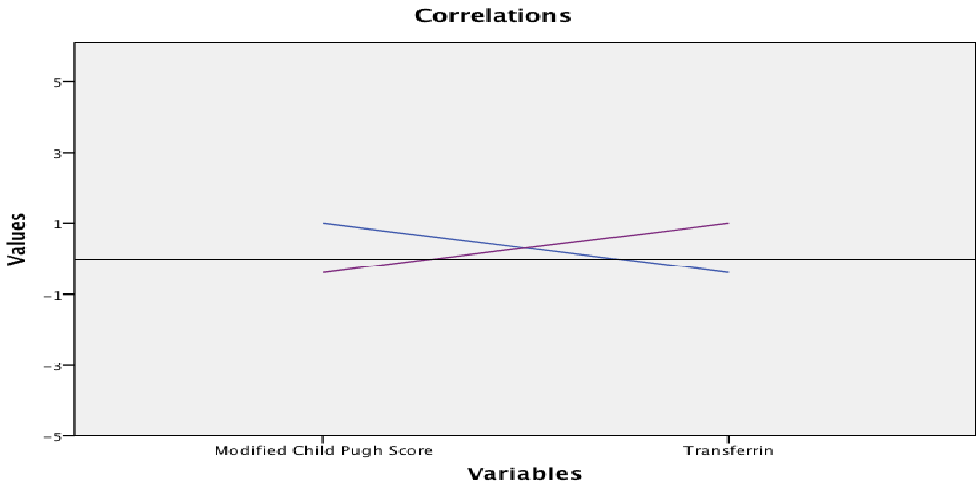
Patients with a low ferritin also had a higher average CPS score of 10.6; these 8 patients all had an upper GI bleed and hence more severe disease.

Transferrin is an iron binding glycoprotein synthesized by the liver that transports iron to various tissues. As a part of the iron profile it was estimated in all 50 patients.

Table 23: TRANSFERRIN LEVELS IN DCLD



20 patients had a normal transferrin levels with an average CPS of 8.4 while 2 patients had higher than normal values with a lower CPS of 8. As the transferrin levels decreased the severity of liver disease was higher, reflected by a higher CPS. This was stastically significant (P value: .004). This shows a negative correlation between Transferrin and severity of disease



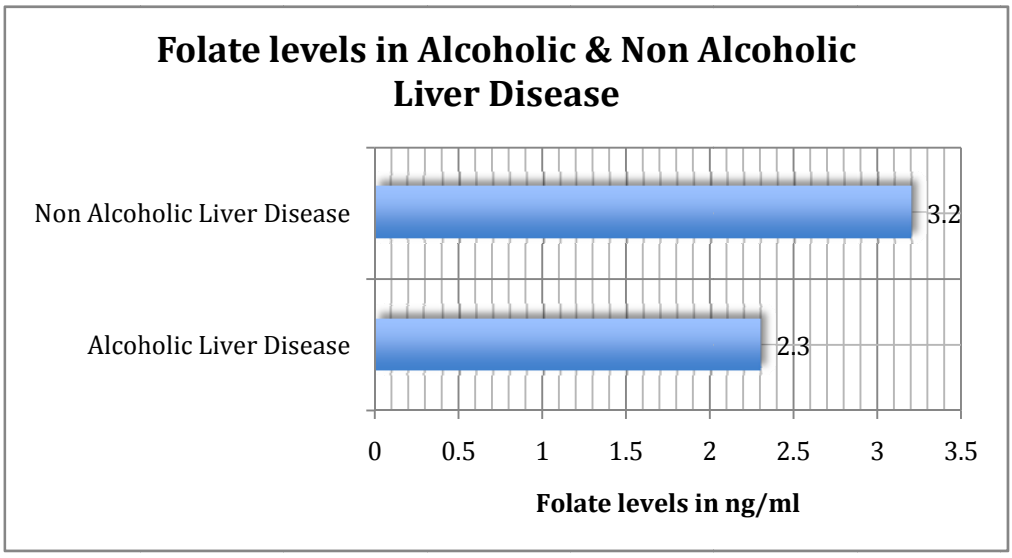
FOLATE LEVELS

All 50 patients were assessed for folate levels. Only 2 patients had normal levels above 5.38 ng/ml. 16 patients had mild deficiency and 32 patients had severe deficiency below 3 ng/ml. The levels did show any correlation with CPS; however the average folate levels of patients with alcoholic liver disease(26) were much lower nonalcoholic(24) DCLD P value – 0.03

Table 24: FOLATE LEVELS IN DCLD

FOLATE LEVELS	*Number of patients*
>5.38	2
3.1 to 5.38	16
<3	32

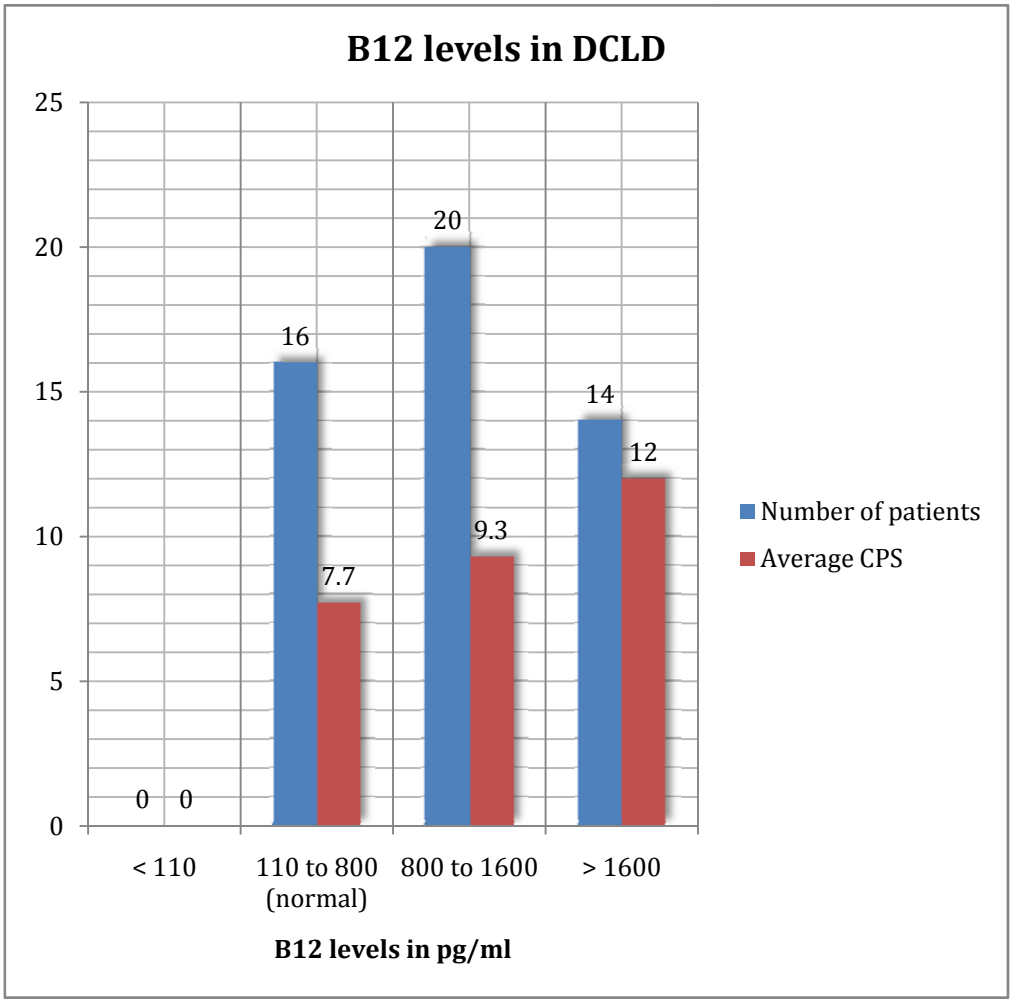
Table 25: FOLATE LEVELS IN ALCOHOLIC & NON-ALCOHOLIC LIVER DISEASE



VITAMIN B12 LEVELS IN DCLD

Vitamin B12 levels were also estimated in all patients. 16 patients had normal B12 levels whereas 34 patients had elevated levels. None had low levels of B12. It was seen that as the B12 levels rose the average CPS also rose, indicating stastically significant correlation between B12 levels and severity of liver disease (P value – 0.001)

Table 26: VITAMIN B12 LEVELS IN DCLD



WBC ABNORMALITIES

The analysis of WBC was done with total and differential counts. Counts ranged from 2700 to 20800.

Table 27: WBC COUNT IN DCLD

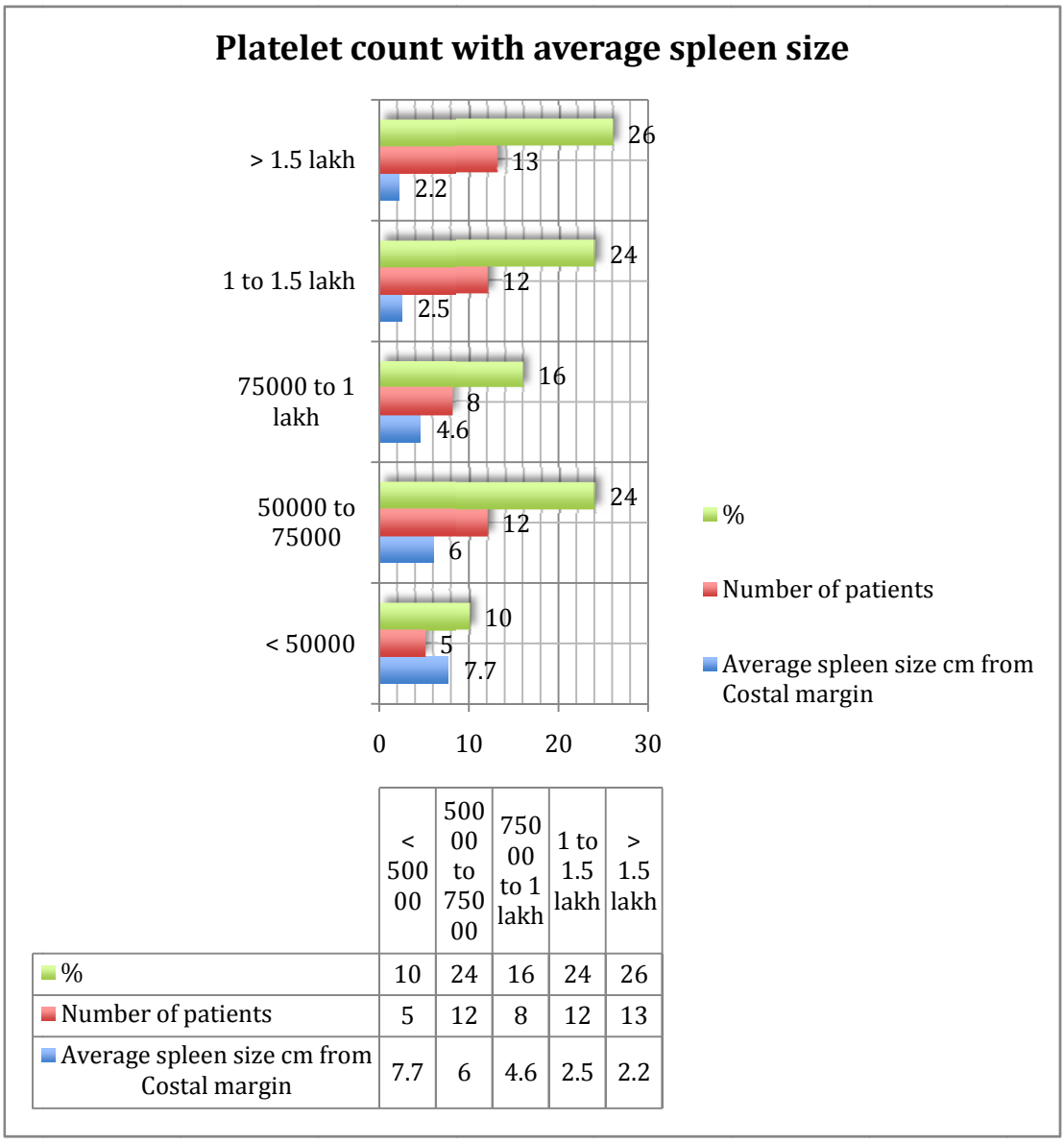
WBC Counts	*Number of patients*
< 4000	13
4000 to 8000	22
8000 to 12000	7
> 12000	8

Among the 50 patients Leucocytosis was observed in 8 patients, 4 patients with a count above 15000 had SBP. The other 4 had low-grade fever probably as a result of endotoxemia. Leucopenia was observed in 13 patients. Eosinophilia was observed in 5 cases, neutrophilia in 8 patients.

PLATELET ABNORMALITIES

50 % of the patients had thrombocytopenia (<1 lakh)

Table 28: PLATELET COUNT COMPARED TO AVERAGE SPLEEN SIZE

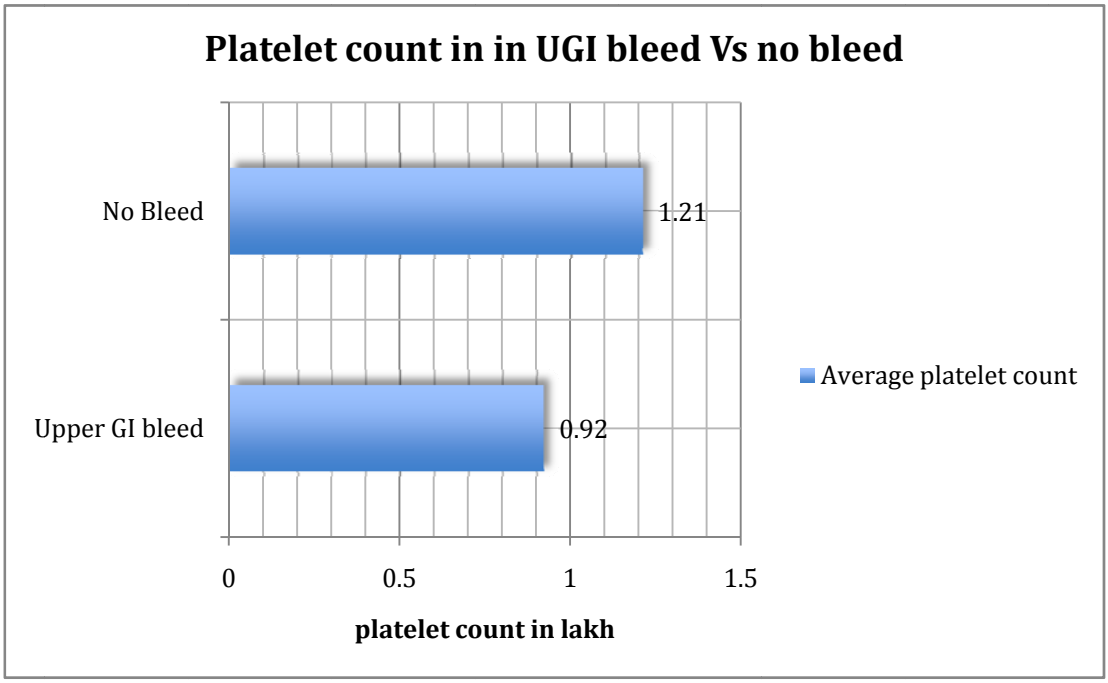


	< 50000	50000 to 75000	75000 to 1 lakh	1 to 1.5 lakh	> 1.5 lakh
%	10	24	16	24	26
Number of patients	5	12	8	12	13
Average spleen size cm from Costal margin	7.7	6	4.6	2.5	2.2

A stastically significant correlation was noted between spleen size and thrombocytopenia (p value – 0.03) Patients with a count less than 50000 had an average spleen size of 7.7 cm.

Of the 13 patients who had an upper GI bleed 3 patients had normal platelet counts and the rest had counts below 1 lakh. The average platelet count of patients who experienced an upper GI bleed was 92000 vs. 1.2 lakh in patients without a GI bleed.

Table 29: COMPARISON OF PLATELET COUNTS IN PATIENTS WITH AND WITHOUT UPPER GI BLEED



The bleeding time was prolonged only in 6 patients with thrombocytopenia indicating BT as an insensitive test. Hypersplenism was noted in 2 patients and 3 patients were found to be in DIC.

COAGULATION PROFILE

The liver secretes all clotting factors except VIII & VWBf. Coagulation profile was assessed using aPTT, PT-INR and fibrinogen levels. 36 patients had a prolonged INR and 6 patients among this group had prolonged APTT. 3 of these patients proved to have DIC with elevated D-dimer and low fibrinogen levels, the other 3 patients probably had dysfibrinogenemia, which is suspected when aPTT is prolonged in the presence of normal fibrinogen levels. Among the 13 patients with upper GI bleed 9 had prolonged INR; indicating other factors play a role in GI bleed. Fibrinogen levels were reduced only in 9 out of 50 patients of whom 3 had DIC.

Table 30: INR VALUES

INR	*Number*
1.3 to 1.6	17
1.7 to 2	10
2 to 2.5	7
>2.5	2

DISCUSSION

This study conducted at Tirunelveli Medical College hospital involving 50 patients has thrown light on many of the hematological abnormalities that is seen in decompensated chronic liver disease.

RBC ABNORMALITIES

According to an article –" Spectrum of anemia associa ted with chronic liver disease by Rosario Gonzalez-Casas, E Anthony Jones, and Ricardo Moreno-Otero" published in the World Journal of Gastroenterology in 2009; anemia of diverse etiology occurs in up to 75 to 80 % of cases of chronic liver disease. The mechanisms operating to produce anemia include the following -

- Haemodilution
- Portal hypertension and splenic sequestration of red cells
- Bleeding into the gastrointestinal tract from varices or bleeding peptic ulcers
- Nutritional deficiencies of folate, B12 and iron
- Suboptimal bone marrow response to chronic inflammation
- Reduced red cell survival
- Alcohol through diverse mechanisms.
- Reduced erythropoietin levels

In our study 90 % of the patients were anaemic; this value is significantly higher compared to the previously cited article. 76 % of the patients had a moderate degree of anemia whereas 14 % of the patients had severe anemia below 6 g/dL.

The changes in Hb, RBC count and Hct parallels each other. The reason for the more severe degree of anemia in this study population of 50 patients could be the following:

- 52 % of patients of this study population had alcoholic liver disease. *Alcohol's adverse effects on the hematopoietic system are both direct and indirect. The direct consequences of excessive alcohol consumption include toxic effects on the bone marrow. Alcohol's indirect effects include nutritional deficiencies that impair the production and function of various blood cells.

In this study the average Hb of patients with alcoholic liver disease was 8.7 g/dL compared to 9.3 g/dL of patients with other causes of DCLD. This clearly shows alcoholism by itself contributes significantly to the causation & burden of anemia.

- This study was undertaken in a Government medical college hospital where all patients belonged to the lower strata of the socio-economic circle; hence they probably had pre existing nutritional deficiencies that added on to burden of chronic liver disease.

Another interesting observation from this study was that males had a higher degree of anemia compared to females. The average Hb of males was 8.9 g/dL compared to 9.1g/dL in females. The reasons probably are

- Males had a more severe liver disease compared to females. The Average CPS of males was 11.2 compared to 8.1 for females

- 11 males had an upper GI bleed compared to only 2 females. In this study the average Hb of patients with an upper GI bleed was 6.5 g/dL compared to 9.8 g/dL with those without a bleed.

- 60 % of the males had alcoholic liver disease compared to no alcoholic liver disease in females.

TYPE OF ANAEMIA

Several studies have been published describing the morphology and frequency of the types of anemia in chronic liver disease; the type of anemia varying in frequency in different studies.

According to Sherlock's textbook of the liver & Oxford textbook of medicine the most common type of anemia is a normochromic normocytic anemia. A Chapter by Atul B Mehta & A Victor Hoffbrand in the postgraduate hematology, fifth edition mentions that 66 % of patients show a macrocytic picture, a view that is shared by Garnet Cheney – "Morphology of the erythrocytes in cirrhosis" published in the California & Western medicine journal 1967. A study by Mishra et al in 1982 said that the most common type of anemia is a normochromic normocytic anemia seen in 79% of the patients.

An article published by Eric William Camille et al in The Journal of French studies & research (volume 17, Number 2, 87-91, April-May-June 2007) elucidates that 43.3 % of patients had a normochromic normocytic anemia where as 20 % had a microcytic hypochromic anemia.

Our particular study conforms more closely to the French study; 44% of the patients had a normochromic normocytic anemia, 30 % had a macrocytic blood picture and 22 had microcytic hypochromic anemia. 16 % of the patients with a microcytic blood picture had an upper GI bleed and one patient with hemochromatosis had sideroblastic anemia that was proven with iron studies and bone marrow.

Various abnormal types of red cells have been described in cirrhosis.

Target cells are bell-shaped RBC that assumes a target shape on dried films of blood. Cooper RA, Arner EC, Wiley JS et al explained that target cells form due to loading of the red cell membrane with cholesterol and lecithin resulting from diminished lecithin cholestrol acyl transferase activity (LCAT). Bile acids are believed to inhibit LCAT activity.

Spur cells or acanthocytes are seen in severe liver disase. They are cells with unusual irregularly placed thorny projections & are believed to be formed from echinocytes or burr cells due to the interaction of abnormal HDL found in liver disease with the red cell membrane (Owen JS, Brown DJ, Harry DS et al – "Erythrocyte Echinocyte in liver disease." Role of abnormal plasma HDL-J Clini. Invst. 1985)

In our study only 3 patients showed target cells and 2 showed acanthocytes. One female patient with Wilsons disease showed few spherocytes suggesting Copper mediated non-immune haemolysis.

IRON STUDIES

Serum iron parameters are affected by liver disorders.

Ferritin is the major iron storage protein in the body. Hepatic parenchymal cells contain appreciable amounts of ferritin, and it is known that liver disease can affect the serum ferritin levels regardless of any change in iron stores. An article published by Elizabeth et al in Ann Intern Med. 15 April 2003; 138(8):627-633 showed correlation between ferritin levels and the degree of hepatic fibrosis.

An article published by A Jacobs and M Norwood in NEJM 1975 showed high ferritin concentrations were associated with severe or active hepatocellular disease.

In our study 28 % of patients had a normal level of ferritin with an average CPS of 8.2. 40 % of the patients had ferritin levels between 292 & 900 ng/ml with an average CPS of 11.05; 16 % of the patients had ferritin levels above 900ng/ml with an average CPS of 13.5;This shows as the ferritin levels rises the severity of liver disease also increases indicating a positive correlation between elevated ferritin levels and liver cell damage. However, even patients with a low ferritin level had a higher CPS than patients with a normal level. This was explained by the fact that all these patients had experienced upper GI bleed and worsening CPS.

Transferrin is an iron binding glycoprotein synthesized by the liver that transports iron to various tissues. In our study the average CPS of patients with a normal transferrin was 8.4; as the transferrin levels decreased the severity of liver disease increased. This showed an inverse correlation between severity of liver disease and transferrin levels. This conforms to the study published by Naciye Şemnur BÜYÜKAŞIK, Işılay NADİR et al in the Turkish journal of gastroenterology 2011; 22 (6): 606-611– "serum iron parameters in cirrhosis" showed a good relationship between severity of parenchymal liver failure and aberrant serum iron test results. Patients with advanced cirrhosis frequently had decreased transferrin levels and elevated ferritin levels.

The overall interpretation of iron studies in relation to anemia should be done cautiously in patients with cirrhosis, as the liver disease itself alters iron parameters, depending on severity. In our study 66 % of patients had a profile showing anemia of chronic disease. 24 % of patients were iron deficient and 10 % had features of iron overload. In patients with iron deficiency ferritin levels were low; however this may be an underestimation of the actual number of cases of iron deficiency because ferritin being an acute phase reactant and being elevated in liver damage may mask iron

deficiency. Hence a better indicator of iron deficiency would be estimation of soluble free transferrin receptor levels in blood which is elevated in iron deficiency independent of liver disease, renal disease or inflammatory state.

4 patients with evidence of iron overload had alcoholic cirrhosis. Alcohol increases iron absorption through two possible mechanisms – increased uptake of iron into hepatocytes in a specific manner through the increased expression of transferrin receptor (TfR) 1; and increased intestinal iron absorption by the lowering of hepcidin (Dysregulation of systemic iron metabolism in alcoholic liver diseases. Kohgo Y, Ohtake T et al: J Gastroenterology Hepatol. 2008)

FOLATE LEVELS

According to a study published by FREDERICK A. KLIPSTEIN and JOHN LINDENBAUM – " folate deficiency in chronic liver disease": Blood 1965 " up to 72 % of patients with chronic liver disease had suboptimal levels of folate in the blood. Alcoholic patients had more severe deficiency compared to other patients.

According to Kurt J. Isselbacher, M.D. and Norton J. Greenberger, M.D. N Engl J Med 1964; a number of mechanisms by which the phenomenon of folic acid deficiency might occur in the alcoholic patient and lead to macrocytic anemia. Decreased intake, impaired intestinal absorption or deranged hepatic metabolism of folic acid might all be involved. Alcohol was shown to inhibit Intestinal conjugase; an enzyme necessary for folate reduction and absorption from the gut.

In our study 96% of patients were folate deficient, 32% having mild deficiency and 64 % having moderate to severe deficiency. However only 30 % of patients had a macrocytic picture. The levels did not correlate with severity of liver

disease. It was stastically proven that patients with alcoholic liver disease had a much lower folic acid levels compared to other causes of CLD.

The average levels of folate in alcoholics were 2.3 ng/ml compared to 3.2 ng/ml in nonalcoholic patients.

Hence our study more or less parallels these western studies but for the fact that a much higher proportion, 96 % of patients had suboptimal folate levels. This can again be accounted by the fact that 52 % of the study population had alcoholic cirrhosis and all patients were from the lower socioeconomic status, probably reflecting a pre-existing nutritional deficiency. It is clear that folate deficiency is very common in cirrhosis patients but more extensive studies correlating bone marrow morphology with folate levels in cirrhotic patients are required before any conclusive results can be drawn regarding contribution of folate deficiency to degree and severity of anaemia in cirrhosis patients.

VITAMIN B12

Several studies have established the fact that Vitamin B12 levels are elevated in patients with chronic liver disease with hepatocellular necrosis.

The mechanisms that were initially postulated include -

-Increased absorption of the vitamin from the gastrointestinal tract

- Altered serum proteins that results in enhanced B12 binding.

- Spurious elevations due to the presence of substances that cross-react with B12

-The release of the vitamin from the liver as a result of hepatocellular damage and necrosis.

A study conducted by Thomas D. Stevenson M.D and Marion F. Beard, M.D. – "Serum Vitamin B12 in liver disease" published in NEJM 1959 investigated the causes of elevated B12 levels in chronic liver disease. Their study using radioactive B12 conclusively showed normal absorption of B12 from the gut, normal serum binding capacity of B12 & normal excretion rates. They concluded by saying the most obvious explanation for the increased serum vitamin B12 content in the presence of liver disease is the release of the vitamin from the liver as the result of hepatocellular necrosis.

The principal evidence for this mechanism from their study is the observation that the serum content was increased only in the presence of hepatocellular disease, declining toward normal with evidence of improvement of hepatocellular function, and that other mechanisms seemed adequately excluded.

In our study 32% of patients had a normal vitamin B12 level with an average CPS of 7.7. 40 % had levels between 800 to 1600 pg/ml with an average CPS of 9.3 & 28 % had levels above 1600 pg/ml with an average CPS of 12.

This clearly indicates that as the severity of liver disease increases the B12 levels rise. This is in accordance to the previously published studies.

WBC ABNORMALITIES

According to Sherlocks textbook of Hepatology, in cirrhosis there is usually a leucopenia in the order of 1500 to 3000 cells/dL. It may be more severe in which case

-Hypersplenism

-Alcohol & cytokine induced bone marrow suppression

-Significant folate deficiency should be ruled out.

Studies by Rosenbloom, A.J. et al published in JAMA in 1995; elevated levels of IL-6 in patients with cirrhosis suggested ongoing leucocyte activation, and predicted the development of a systemic inflammatory response syndrome.

Altin et al have described abnormalities of Neutrophil function – adhesion and chemotaxis accompanied with low levels of C3 in DCLD. Very little is known about the role of granulocyte colony-stimulating factor (G-CSF) or granulocyte macrophage colony-stimulating factor (GM-CSF) in leucopenia associated with cirrhosis. Gurakar et al have shown that GM-CSF treatment for seven days in patients with cirrhosis and leucopenia resulted in an increase in the WBC count.

Hypergammaglobulinemia is almost universal in chronic liver disease. It is due to immunization of the antigen presenting cells with enteric microbes and antigens with resultant lymphocyte activation. IgA is elevated in alcoholic cirrhosis whereas IgG elevated in autoimmune hepatitis.

In our study group of 50 patients the WBC count ranged from 2700 to 20800. 26% of patients had leucopenia with count less than 4000. 58% had normal count & 16 % of patients had Leucocytosis. 4 patients with count above 15000 had proven spontaneous bacterial peritonitis; the other 4 had low-grade fever and severe liver disease probably resulting from endotoxemia.

Eosinophilia was observed in 5 cases probably resulting from underlying parasitic infection.

It was not possible to obtain functional studies of WBC nor electrophoretically determine the type of immunoglobulin's elevated in cirrhosis due to lack of facilities. However all 50 patients had A:G reversal. It was due to both decreased synthesis of albumin with deteriorating liver function and increased synthesis of immunoglobulin.

An interesting observation that was made was the correlation of A:G ratio with severity of liver disease. When the ratio was lower, the severity of liver disease was higher – 6% of patients had A:G ratio of <.05 with an average CPS of 13.6 whereas when the A:G ratio was 0.8 to 0.9 the CPS was 8.3.

PLATELET ABNORMALITIES

Several studies on platelet defects in DCLD have been done before. According to an interesting article by Jody L Kujovich MD – "Haemostatic defects in end stage liver disease "; Critical care clinics 21 (2005) - mild to moderate thrombocytopenia occurs in 49 to 64 % of patients with DCLD. The platelet count is rarely less than 30 to 40 thousand. The etiology of thrombocytopenia is multifactorial –

- Splenic sequestration of platelets
- Low Thrombopoietin levels
-Hypersplenism
-Reduced platelet half-life related to autoantibodies
- Folate deficiency
- Alcohol induced bone marrow suppression
- DIC
- Sepsis
- Drugs

Functional platelet defects are well described in several studies.

Escolar G et al reports that platelet aggregation seems to be particularly affected in as much as 46% of patients with DCLD.

The possible mechanisms have been postulated by a study by Ballard HS, Marcus AJ et al - "Platelet aggregation in portal cirrhosis"; Arch Intern Med 1976. They include

- Reduced availability of arachidonic acid for prostaglandin synthesis
- Reduced platelet ATP and serotonin
- Circulating factors that inhibits platelet aggregation - FDP and D- dimers, plasmin degradation of platelet receptors, dysfibrinogenemia, and excess nitric oxide synthesis.
- Nitric oxide is a powerful vasodilator and inhibitor of platelet adhesion and aggregation produced by vascular endothelial cells.
- HDL isolated from cirrhotic patients inhibit ADP induced platelet aggregation
- Platelet binding domains are abnormal thus preventing efficient binding to Von Willi Brand factor during adhesion.

Comparison of various studies showed conflicting reports regarding bleeding time as a test to assess platelet function adequately. Blake JC et al." Bleeding time in patients with hepatic cirrhosis". BMJ 1990 reports that bleeding time is prolonged in as much as 40% of patients with cirrhosis. However another study by Basili S et al. "Bleeding time does not predict gastrointestinal bleeding in patients with cirrhosis"; J Hepatol (1996) reports bleeding time as an inadequate and ineffective test for platelet function and correlates poorly with bleeding tendency.

In our particular study 50% of patients had thrombocytopenia (< 1 lakh) of which 80% had mild to moderate thrombocytopenia (50 to 100 thousand). This conforms to the article by Jody L Kujovich mentioned earlier. The rest 20 % had severe thrombocytopenia (below 50000).

Our study also compared the degree of thrombocytopenia to the spleen size clinically palpable from the costal margin. The average spleen size of patients with count between 75 to 100 thousand was 4.6 cm, those with a count of 50 to 75 thousand was 6cm and those with a count less than 50000 had an average spleen size of 7.7 cm. According to a study by Aster RH et al "Pooling of platelets in the spleen" J Clin Invest 1966 the normal spleen sequesters up-to 33% of the platelet mass exchanging freely with circulating platelets. Markedly enlarged spleens may sequester up-to 90 % of platelets. This report conforms closely with our study.

In our study, of the 13 patients who had an upper GI bleed, 3 patients had normal platelet counts and the rest had average platelet count of 92000. The bleeding time was prolonged only in 12% of patients with thrombocytopenia. This clearly indicates that bleeding time as an insensitive test for platelet function conforming to the result shared by Basili S et al; and functional abnormalities probably play a role. However due to lack of facilities platelet functional studies could not be taken up.

COAGULATION ABNORMALITIES

A deranged coagulation system is very common in chronic liver disease. There is reduced synthesis of all coagulation factors (except factor VIII & Von Willi Brand factor), Vitamin K deficiency, Hyperfibrinolysis & dysfibrinogenemia, all contributing to increased bleeding tendency.

Tripodi et al HEPATOLOGY 2005 through an elegant study have shown in addition to the diminished hepatic synthesis of clotting factors, patients also have a profound deficit of natural anticoagulants, mainly of protein C (a protein synthesized by the liver), and also of anti-thrombin, which may counterbalance the bleeding tendency caused by the deficiency in procoagulants. This was the concept of the

Rebalanced Haemostatic system, which can be tipped in favor of bleeding or thrombosis depending on the clinical situation.

In our particular study as much as 72% of patients had a prolonged PT-INR and 6 patients within this group had a prolonged aPTT, though only 25 % of these patients had an upper GI bleed. This may suggest a rebalanced coagulation system in action to prevent bleed, however we did not have any patient with DCLD who presented with thrombosis. Individual assessment of procoagulants & endogenous anticoagulants were not possible due to lack of facilities and are definitely warranted for more conclusive results.

According to Bakker CM et al "Disseminated intravascular coagulation in liver cirrhosis" J Hepatol 1992 low grade DIC is a feature in upto 7 to 25 % of patients with cirrhosis particularly Child C cirrhosis. In our study only 6% of patients were in DIC, all patients suffering from spontaneous bacterial peritonitis and sepsis.

Thus from this limited study of 50 patients with decompensated chronic liver disease we were able to draw many inferences regarding the haematological abnormalities that contribute to the morbidity of patients.

Many of the results obtained conform to previously done studies mentioned earlier but whether these results can be extrapolated to the larger population of cirrhotic patients as a whole is not definitely known and needs larger, more comprehensive studies with a wider range of patient selection.

CONCLUSIONS

Many conclusive results regarding the haematological abnormalities in decompensated chronic liver disease were obtained with this limited study involving 50 patients with decompensated cirrhosis

⇒ 90% of the patients were anaemic of whom 14% had severe anaemia with a Hb less than 6 g/dL

⇒ The changes in Hb, RBCcount and Haematocrit parallel each other with haemodilution evident at each given level of Hb & RBC count

⇒ In this study males had a worse Hb, RBC count and haematocrit compared to females

⇒ Patients with an upper GI bleed had significantly lower levels than patients without bleed.

⇒ The average Hb of alcoholic cirrhosis patients was 8.7 g/dL compared to 9.3g/dl of non-alcoholic cirrhosis indicating alcohol by itself worsens the haematological profile

⇒ The most common type of anaemia was a normochromic normocytic anemia seen in 44% of patients

⇒ Macrocytic picture was seen in 30% of patients; majority (93%) of whom were alcoholics

⇒ 22% patients had microcytic hypochromic anaemia of which roughly 73% patients had an upper GI bleed. One patient had hemochromatosis; further evaluation of this patient revealed him to have sideroblastic anemia. Dimorphic picture was observed only in 4 % of cases.

⇒ Ferritin levels were elevated as the severity of liver disease progressed and was shown to be stastically significant

⇒ Transferrin levels decreased as the severity of liver disease increased showing an inverse relation between the two.

⇒ Interpretation of iron studies revealed that the most common type of anemia was anemia of chronic disease seen in 66% of patients. Iron deficiency was seen in 24% of patients and iron overload seen in 10% of patients. Elevated ferritin levels may mask the actual number of cases of iron deficiency; hence soluble transferrin receptor levels need to be measured to get a true estimate of iron deficiency. Iron overload is seen in alcoholic patients and the one patient with hemochromatosis.

⇒ 96 % of patients were folate deficient, alcoholics being significantly more deficient than non-alcoholic cirrhosis.

⇒ Vitamin B12 levels were elevated in 68 % of patients and correlated significantly with severity of liver disease.

⇒ 44 % of patients had a normal WBC count. 26 % had low counts below 4000. Only 16% of patients had a count above 12000 of which 50% had spontaneous bacterial peritonitis.

⇒ 50 % of patients had thrombocytopenia.

⇒ The severity of thrombocytopenia had good correlation with spleen size

⇒ The average platelet count of patients with an upper GI bleed was 92000 compared to 1.2 lakh to those without an upper GI bleed; suggesting other factors such functional platelet defects may play a role as well. These need to be confirmed with platelet functional studies.

⇒ Bleeding time was prolonged only in 12 % of patients with thrombocytopenia indicating BT as an insensitive test of platelet number and function.

⇒ The PT-INR was elevated in 72 % of patients, of which 12 % also had an elevated aPTT. However only 25 % of patients with a prolonged PT-INR had upper GI bleed indicating other factors such as a rebalanced hemostatic system at work, however this needs to be confirmed with more extensive studies. This result underlines the fact that clinical status of the patient and not lab values have to be treated, when correcting coagulopathy in a patient with cirrhosis.

From this study we can conclude that various haematological alterations are very common in cirrhosis patients that needs to be identified and corrected early to reduce morbidity and mortality.

POTENTIAL FUTURE STUDIES

1. Erythropoietin, Thrombopoietin levels and adequacy of bone marrow response in decompensated chronic liver disease.
2. Functional abnormalities of WBC in decompensated chronic liver disease
3. Functional platelet abnormalities in chronic liver disease
4. Assessment of individual procoagulant and anticoagulant factors in decompensated chronic liver disease.

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PROFORMA

Name Age Sex IP No.

Occupation Address

Presenting complaints

History of present illness

Jaundice Pedal edemaAscites

Abdominal painNausea Vomiting

FeverHemetemesis/MelenaLOC/Fits/Confusion

OliguriaChest painConstipation/diarrhoea

Other symptoms

Past H/o.

DiabetesJaundice

Hypertension Trauma

Ischemic heart disease Blood transfusion

Tuberculosis Seizures/involuntary movements

Bronchial asthma Needle prick

Chronic kidney disease Surgery

Malignancy Drugs

Personal H/o.

Diet

Marriage statusSmoker

AlcoholIv drug abuseSexual history

Family H/o

CLDWilson'sHealth of members of family

Clinical examination

General examination

Built Clubbing

Nourishment Cyanosis

Conscious Pedal edema

Oriented Lymphadenopathy

AnaemiaJaundice

Stigmata of CLD:

Face Hands

TelengectasiaWhite nails

Xanthelasma Palmar erythema

KF ring Duputyren's contracture

Parotid enlargement

Paper money skin

Loss of eye brows

Jaundice

Endocrine Skin

GynaecomastiaSpider nevi

Testicular atrophy scanty body hairSlate gray pigmentation

Scratch marks

Vital signs

PulseBlood pressureTemperatureRespiratory rate

Systemic examination

CVS

RS

CNS: Level of consciousnessFlapping tremorsPlantar reflex Constructional apraxia

ABDOMEN:

Ascites Divarication of recti

Liver Umbilical hernia

Splenomegaly

Dilated veins over abdomenHernia and Hydrocele

Investigations

Blood

TC **Liver function test**

DC S. Bilirubin

ESR SGOT

HbSGPT

RBC Count SAP Total protein / Albumin

PCV

MCV MCHMCHC

Platelet count

Sugar Blood ureaCreatinine Sodium Potassium

BT PT-INR - APTT

Peripheral smear for blood picture

Reticulocyte count

Ascitic fluid:

Biochemical analysisCytologyCell countsFluid C/s

Chest X-rayECG in all leadsUltrasound abdomen and pelvis

Viral markers

HBS Ag, Anti HCV antibody

USG ABDOMENUGI ENDOSCOPY

Iron studies Folate levelsB12 level –

Serum iron

Ferritin

Transferrin

Transferrin saturation

TIBC

Measure	1 point	2 points	3 points
Total bilirubin,(mg/dl)	(</=2)	(2-3)	(>3)
Serum albumin, g/l	>35	28-35	<28
PT INR	<1.7	1.71-2.30	> 2.30
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)

Total score -

Master Chart

Sl No	NAME	IP No:	Age	Sex	symptoms & signs					risk factors		Diagnosis	Complete Blood Count									P.Smear/Retic Count	Iron Studies						Folate (>5.38ng/ml)	B12(110 to 800 pg/ml)	PT (12 to 16s/ INR (<1.3)	BT (2 to 8Mins)	APTT (21 to 29s)Control - 24.6	Fibrinogen (150 to 400mcg/dL)	Liver Function Tests									Ascites	HEPATIC ENCEPHALOPATHY	Modified Child Pugh score (CPS)
					abdominal distension	jaundice	hematemesis/malena	altered consciousness	Splenomegaly (cm below CM)	past h/o jaundice	alcoholism		HB (gm/dL)	TC (per cmm)	DC (P/L/E)	RBC Count (cells/Cumm)	PCV	MCV	MCH	MCHC	PLT		Ferritin 10 to 291(ng/ml)	Iron (50 to 170mcg/dL)	TIBC (250 to 450mcg/dL)	Transferrin (176 to 280mcg/dL)	T.Sat (20 to 50 %)	Inference						TB	DB	IB	SGOT	SGPT	ALP	TP	Alb	Glob			
1	Marimuthu	44243	32	M	yes	yes	no	yes	3	no	yes	Alcoholic Liver Disease.DCLD, Portal HTN,Hepatic Encephalopathy	7.8	12400	83/15/2	2.8	23.3	106.9	39.8	35.5	1.53	Macrocytic Blood Picture/0,4%	509	32	93	73.2	34.40%	ACD	2.27	1748	25.9/2.09	7	40	112	14	8	6	92	380	158	7.7	3	4.7	SEVERE	II	12
2	Parvathy	45567	45	F	yes	yes	yes	no	9	no	no	DCLD, portal hypertension, hypersplenism, autoimmune, UGI bleed.	4.1	3800	64/27/9	1.9	15.1	74.8	20.3	27.2	0.25	hypochromic microcytic cells with reduced platelets	16.9	28	325	256	8.70%	IDA	3.18	234	15.6/1.3	10	30	160	3	1.8	1.2	86	50	72	7.1	3	4.1	MILD	0	9
3	Govindan	4485	50	M	yes	yes	no	yes	2	yes	yes	Alcoholic liver disease, DCLD, portal hypertension, hepatic encephalopathy, HRS	5.5	20800	84/16	2.4	18	84	25.6	30.6	3.19	normocytic normochromic cells/0.7	1650	110	111	87	10%	ACD	1.59	>2000	2.46	4	28	90	25	20	5	15	36	46	10.6	3.5	7.1	SEVERE	II	12
4	Murugan	47221	52	M	yes	no	no	no	4	yes	no	Alcoholic liver disease, DCLD, portal hypertension	5.6	14800	80/20	2.3	19	119	37.2	37.1	0.98	macrocytic picture / 0.6%	520	30	90	110	30%	ACD	1.37	1001	1.2	6	28	168	9.2	5.6	3.2	30	46	110	5.9	1.6	4.3	SEVERE	0	12
5	Mupidathi	57314	58	M	no	no	yes	yes	2	yes	no	DCLD, HBsAg positive, portal hypertension, hepatic encephalopathy, UGI bleed	7.2	3600	70/30	2.7	28	72	26	27	1.6	microcytic hypochromic / 1%	5.5	17	321	178	5.2	IDA	3.51	718	1.1	6	26	280	2.4	1.8	0.6	42	38	82	6.8	3	3.8	MILD	I	9
6	Thirviyam	47377	40	M	no	no	yes	yes	3	no	no	DCLC, ? Cause, portal HTN, HE, UGI bleed	5.2	4700	50/40/7/3	2.1	16.6	95.6	29.8	32	1.2	normocytic normochromic anaemia with mild thrombocytopenia / 1%	509	32	93	73.2	34.40%	ACD	2.2	1748	1.2	4	25	300	2.2	1.1	1.1	48	36	92	5.8	2.8	3	MILD	I	9
7	Bhagavathi	87177	65	F	no	no	no	no	2	yes	no	DCLD, hepatitis B, portal HTN	10.1	3800	60/36/4	4.1	30	70	24	27	3.8	microcytic hypochromic cells / 0.8%	20.3	46	387	305	11.80%	IDA	3.43	1255	1.4	3	30	276	1.2	0.8	0.4	36	38	28	6.2	3	3.2	MILD	0	7
8	Chinnathamb	53817	55	M	Yes	yes	no	yes	2	yes	yes	Alcoholic liver disease, DCLD, Portal HTN, HE	10.8	3900	70/30	4.3	36	110	28	30	1.4	macrocytic cells with target cells	272	54	77	56.6		ACD	2.1	1418	2.4	5	32	98	4.8	2.8	2	57	30	92	5.8	1.4	4.4	SEVERE	II	13

9	murugaiah	11456	35	M	yes	yes	no	yes	2	no	yes	Alcoholic liver disease, DCLD, Portal HTN, HE,SBP	5.4	19300	78/20/2	2.2	15.4	54.5	38.8	35	1.5	macrocytic cells with mild anisocytosis, target cells, acanthocytes, lecucytosis with left shift	322	83	62	48	110%	ACD	1.32	633	2.8	3.5	40	90	6	4	2	54	80	92	5.4	2	3.4	SEVERE	IV	14
10	havasipandiya	36177	45	M	no	no	no	no	2	no	yes	Alcoholic liver disease, DCLD, Portal HTN	11.2	3400	70/30	4.5	39	58	30	33	2 lac	normocytic normochromic	1650	70	36	28		ACD	1.24	2000	1.4	2	30	360	3.2	1.2	2	60	66	80	6.2	3.1	3.1	MILD	0	9
11	Hariram	24679	58	M	no	no	no	no	5	no	yes	ALD, cirrhosis, portal HTN	9.1	9100	55/40/5	3.4	29.7	100.3	31.4	32	0.58	macrocytic picture with poikilocytosis / 0.8%	79.1	40	201	158	41.80%	ACD	3.32	1021	6	1.6	30	168	3	2	1	48	46	92	6.8	3	3.8	MILD	none	8
12	Ramar	26510	50	M	yes	yes	no	yes	3	yes	no	DCLD, Hepatits B, portal HTN, HE	9.8	6000	60/30/10	3.6	30	88	30	31	1.2 lacs	normochromic, normocytic / 0.9%	1650	110	111	212	51	ACD	1.59	2000	5	1.8	29	240	4.2	2	2.2	48	46	90	7.1	3.5	3.6	MILD	II	10
13	Thangaraj	17671	59	M	no	no	no	no	2	no	no	DCLD ? CAUSE. Portal HTN	12.2	6200	60/34/6	4.6	34.3	90.4	22.1	35.5	1.52	normochromic normocytic with few hypochromic cells / 1%	59	37	168	168	27.7	ACD	4.62	762	4	1.2	54	300	2.1	1	1.1	46	40	87	7.6	3.4	4.2	MILD	none	7
14	Sangeetha	42526	38	F	no	no	no	no	2	no	no	DCLD, autoimmmune hepatitis, portal HTN	12.8	7000	70/30	4.8	40	98	31	33	2.8	normochromic nomocytic / 1%	128.2	66	233	183	28%	normal status	5.69	562	4	1.2	26	225	1.6	0.2	1.4	40	40	80	7	3	4	MILD	none	6
15	Chandran	47741	40	M	yes	yes	no	yes	8	yes	yes	ALD, cirrhosis, portal HTN, HE	13.3	6000	85/15	4.8	40.6	100.7	33	32.8	0.58	macrocytic picture / 1%	310	28	210	170	13.30%	ACD	1.26	1000	5	1.3	27	314	4.5	1.5	3	61	208	276	6.7	3	3.7	MILD	II	10
16	Pattu	46451	45	M	no	no	yes	no	7	no	no	DCLD ? CAUSE. Portal HTN, UGI bleed	7.5	7300	77/12/11	2.6	24.8	72.1	26	27	0.68	microcytic hypochromic / 1.2%	7.4	36	260	156	13.80%	IDA	1.1	568	4	1.3	25	218	0.6	0.3	0.3	75	65	471	6.7	3	3.7	MILD	none	7
17	Ramalingam	42966	51	M	no	no	yes	yes	2	no	yes	ALD, cirrhosis, portal HTN, UGI bleed, folate and iron deficiency	6.7	6100	63/27/10	2.1	23	68.2	19.9	29.1	3.9	dimorphic picture / 0.8%	161	36	210	157	17%	IDA	1.2	970	5	1.2	28	283	1.3	0.7	0.6	30	37	195	6.2	3	3.2	MILD	none	7
18	Kanagaraj	25234	33	M	no	no	no	no	3	no	no	DCLD, portal HTN ? Autoimmune	10.6	10300	51/38/11	3.8	32.7	87	28	33	1.2	normochromic normocytic / 1.2%	721	36	240	138	15%	normal status	2.5	620	4	1.3	28	312	2	1.4	0.6	37	133	47	5.4	2.2	3.2	MILD	none	8
19	marimuthu	26910	39	F	no	no	no	no	4	no	no	DCLD, cirrhosis ? Cause, portal HTN	12.8	7000	70/20/10	5.2	28	92	30	32	1.6	normochromic normocytic / 1.2%	160.9	168	192	157	58%	normal status	4.5	721	5	1.2	27	300	1.4	0.7	0.5	40	46	88	6.4	3	3.4	MILD	none	7
20	John	53135	42	M	yes	yes	no	yes	3	yes	yes	ALD, cirrhosis, portal HTN, grade 2 HE, SBP	10.6	18700	88/10/2	4.3	34.3	98	30.5	30.9	1.25	normochromic normocytic with reactvive neutrophils and toxic granules	618	36	230	170	18%	ACD	3	900	6	1.5	30	314	3.4	1.4	2	62	107	193	7.8	3.3	4.5	MOD	II	10
21	Subbulakshm	47781	70	F	yes	yes	yes	yes	10	yes	no	DCLD, cirrhosis ? Cause, portal HTN, HE, hypersplenism	5	2700	65/35	2.2	21	88	30	33	0.36	normocytic normochromic , decreased platelets / 2%	1200	36	200	143	218%	ACD	1.2	1650	12	1.8	36	120	8	3	5	76	38	164	5.4	1.8	3.6	MOD	III	14
22	Basheer	97761	56	M	no	yes	no	no	7	no	yes	DCLD, ALD, portal HTN	13.3	6000	65/35	5.4	40.6	106.7	33	37.8	0.62	macrocytic picture / 0.6%	300	28	274	190	10%	ACD	3.6	834	4	1.6	26	240	4.5	1.5	3	81	66	70	6.3	3	3.3	MILD	none	9

23	Ravanan	47777	55	M	yes	yes	yes	yes	5	yes	no	DCLD, cirrhosis, hepatitis C, portal HTN, massive UGI Bleed, HE	5.5	7700	86/14	2.8	18.5	70.2	20.2	24	0.98	microcytic hypochromic / 1.1%	12	30	260	300	10%	IDA	1.8	760	4.5	1.6	28	280	0.9	0.3	0.6	70	60	110	6.6	3	3.6	MILD	II	9
24	Jagdish	56321	46	M	no	no	yes	yes	8	no	no	DCLD, cirrhosis ? Cause, portal HTN, HE, UGI bleed	7.5	7300	79/12/9	3.1	24.8	84.1	30.2	34.1	0.56	normochromic normocytic / 0.7%	16	24	200	200	7%	IDA	3.2	500	4	1.7	29	210	1.1	0.5	0.6	28	48	104	6.9	3	3.9	MILD	II	9
25	Raja	65784	24	M	yes	no	no	no	6	no	no	DCLD, cirrhosis, Hemochromatosis, portal HTN, sideroblastic anaemia, DKA	4.8	9800	60/30/10	2.1	26	78	28	27	0.6	microcytic hypochromic / 0.6%	1100	430	450	250	95%	IRON OVERLOAD	4.8	960	5	2.1	31	120	3.2	1	2.2	50	60	92	6.8	3	3.8	MOD	II	11
26	Chandran	46452	46	M	no	no	no	yes	2	no	yes	ALD, cirrhosis, portal HTN, HE	10.8	9000	60/30/10	3.8	28	101.4	35	33	1.6	macrocytic picture / 0.6%	601	40	103	86.4	39%	ACD	2.8	1450	3	1.6	29	200	1.8	0.8	1	54	68	110	7	3	4	MILD	I	8
27	Sivagasan	58521	40	M	no	no	no	no	3	no	no	DCLD, cirrhosis ? Cause, portal HTN	11.2	7000	70/20/10	4	33	93.2	30	32	1.62	normochromic normocytic / 1%	680	210	300	200	70%	IRON OVERLOAD	3.6	708	6	1.7	28	260	1.4	0.6	0.8	86	80	70	7.1	3	4.1	MILD	0	8
28	Ramalingam	94848	49	M	no	no	no	no	4	no	yes	DCLD, cirrhosis, hepatits B, alcoholism, portal HTN	8.4	4300	68/30/2	2.7	29	86	28	30	0.96	dimorphic picture	900	110	216	230	49%	ACD	2.4	930	7	1.6	30	158	2	1	1	96	80	110	6.8	3	3.8	MOD	II	10
29	Manikandan	56103	62	M	yes	yes	yes	yes	3	yes	yes	ALD, cirrhosis, portal HTN, HE, UGI bleed	7.1	5000	70/30	2.1	27	77	26	25	0.82	microcytic htpochromic/ 0.8%	10	26	325	260	8%	IDA	4.5	760	6	1.9	28	140	4.1	2.1	2	48	112	110	7	3	4	MOD	III	13
30	Saravanan	52621	41	M	yes	yes	no	yes	2	no	no	DCLD, cirrhosis ? Cause , portal HTN, SBP, HE	10.4	16800	84/16	3.4	32	89	28	29	1.78	normochromic normocytic with neutrophilic leucocytosis/1 %	1200	116	210	186	55%	ACD	5.8	640	4	1.6	25	287	3.1	1	2.1	48	56	116	6.8	2.8	4	MOD	I	11
31	velumani	70353	39	M	no	no	no	no	5	no	yes	ALD, cirrhosis, portal HTN	11.6	4500	70/30	4.8	36	110	30	32	0.84	macrocytic picture / 0.6%	361	54	216	250	21%	ACD	2.9	920	4	5	25	160	2.2	1	1.2	46	124	130	7.2	3.2	4	MILD	0	8
32	Jayashankar	94848	52	M	no	no	yes	no	6	no	yes	ALD, cirrhosis, portal HTN, UGI bleed, hypersplenism	6.5	3800	50/40/10	2.1	17.2	73.1	38	26	0.56	microcytic hypochromic/ 1.2%	12.1	25	329	280	2%	IDA	2.6	760	6	9	26	240	1.6	0.8	0.8	54	130	110	6.8	3	2.4	MILD	0	7
33	Muniandi	70352	50	M	yes	yes	no	yes	2	no	yes	ALD, cirrhosis, portal HTN, HE	10.8	3900	0/30/10/1	3.2	34	108	28	30	1.4	macrocytic picture, targecells seen	270	54	76	68	74%	IRON OVERLOAD	1.4	1116	5	1.7	28	168	2.8	0.8	2	47	80	96	6	2.4	3.6	MOD	II	11
34	Selvam	90281	63	M	yes	yes	no	yes	3	yes	yes	ALD, cirrhosis, portal hypertension, SBP, HE	9.8	13400	90/5/5	3.3	28	111	27	28	1.5	macrocytosis, anisocytosis, target cells, acanthocytosis, leucocytosis with left shift	322	80	264	50	30%	ACD	1.4	980	4	2	30	116	3.4	1	2.4	54	30	92	6.8	3	3.8	MOD	III	13
35	Muthusamy	30128	50	M	no	no	no	no	3	no	no	Cirrhosis, portal HTN ? Cause	9.2	9100	55/40/5	3.1	29.7	100.3	31.2	30	1.4	macrocytosis/ 0.8%	79.1	40	201	156	42%	ACD	2.4	1021	6	1.6	30	168	2	1	1	48	96	92	6.8	3	3.8	MILD	none	8
36	Rajamuthu	72911	45	M	no	yes	no	yes	2	no	yes	DCLD, cirrhosis, ALD, portal HTN, HE	10.1	6000	60/40	3.5	30	86	30	31	1.2	normochromic normocytic/1. 1%	1650	110	316	212	33%	ACD	1.56	>2000	4	1.8	28	240	3.1	2	1.2	48	46	90	7.1	3.5	3.6	MILD	II	10

37	Veeramani	35051	58	M	no	yes	no	yes	6	yes	yes	ALD, cirrhosis, portal HTN, HE	12.1	4800	80/20	4.7	41.6	116	34	31.6	0.8	MACROCYTIC PICTURE / 1%	310	28	210	170	14%	ACD	1.36	1000	5	4.5	27	314	4.5	1.5	3	61	208	276	6.7	3	3.7	MILD	II	10
38	Subramanian	37736	46	M	no	no	yes	no	7	no	yes	ALD, cirrhosis, PORTAL HTN, UGI bleed	7.6	7300	79/12/9	2.6	24.8	70.1	26	27	0.7	micricytic hypochromic / 1%	7.4	36	260	176	14%	IDA	1.4	68	4	5	26	218	0.6	0.3	0.3	75	65	471	6.7	3	3.7	MILD	none	7
39	Murugan	70149	28	M	no	no	no	yes	2	no	no	Cirrhosis, portal HTN ? Cause, HE	10.1	9300	57/38/5	4.1	32.7	87	28	23	1.1	NORMOCHROMIC NORMOCYTIC / 1.1%	722	35	240	138	15%	ACD	2.5	620	4	1.3	28	312	2	1.4	0.4	37	133	47	5.4	3.6	1.8	MILD	none	8
40	Rajamani	50513	46	M	yes	no	no	yes	2	no	yes	ALD, cirrhosis, portal HTN ,HE, SBP	10.6	15000	90/10	4.2	34.3	88.6	30.5	31	1.25	normochromic normocytic	618	36	240	176	15%	ACD	3	900	3	1.5	29	214	2.1	1.1	1	62	50	112	7.8	3.3	4.5	MOD	II	11
41	Nalini	44712	32	F	no	yes	no	no	2	yes	no	Wilsons disease	9.2	8800	60/40	3.6	38	90	30	37	1.6	normocytic normochromic cells; few spherocytes seen	416	56	318	260	18%	ACD	2.1	460	2	1.6	285	300	3.1	0.2	2.9	40	180	160	7.6	3	4.6	MILD	none	7
42	sunderaajan	51631	58	M	yes	no	no	yes	6	yes	no	cirrhosis liver, hepatitis B, portal HTN, HEPATIC ENCEPHALOPATHY I	10.6	7100	65/35	4.9	40.6	91	28	30	0.8	normocytic normochromic cells	456	63	316	200	20%	ACD	4.2	680	8	8	265	116	2.1	0.1	2	40	46	160	6.6	3	3.6	MOD	I	10
43	Karuppasamy	17482	52	M	yes	no	yes	yes	4	no	no	DCLD, cirrhosis ? Cause, portal HTN, HE, UGI bleed	7.5	4000	60/40	2.4	21.2	68.6	21	23	0.7	microcytic hypochromic anaemia / 1%	9	80	260	176	12%	IDA	2.21	960	4	8.5	30	300	2.2	1	1.2	46	124	130	6.8	3	3.8	MOD	II	11
44	Vijay anand	17688	69	M	no	no	no	no	4	no	yes	Alcoholic liver disease, Cirrhosis, portal HTN	9.8	3200	60/30/10	3.2	36	80	28	30	0.76	normocytic normochromic anaemia / 1%	260	150	300	180	50%	IRON OVERLOAD	2.8	760	6	6	27	316	1.8	0.8	1	58	98	100	7.1	3.5	3.6	MILD	0	6
45	Rajeshwari	45451	46	F	no	no	no	no	4	no	no	cirrhosis liver ? Cause, portal HTN	10.1	4600	70/28/2	3.6	38	98	29	31	0.88	normocytic normochromic cells	290	50	350	190	15%	ACD	4.6	800	7	10	25	400	1.4	0.7	0.7	46	54	110	6	2.8	3.2	MILD	0	6
46	Arun	50993	51	M	yes	no	no	yes	6	no	yes	ALD, cirrhosis, portal HTN, HE	8.8	3200	63/15	3.3	21	102	30	32	0.65	macrocytic blood picture / 0.4%	512	36	94	73.2	34%	ACD	2.7	1860	4	11	31	116	3.8	1.8	2	92	350	158	7	3	4	MOD	II	12
47	Subbiah	51319	45	M	no	yes	yes	yes	10	no	yes	ALD, cirrhosis, portal HTN, UGI bleed, HE grade II	7.1	3000	60/30/6	2.7	16	74.8	21	27	0.36	microcytic hypochromic cells with low platelets / 0.5%	16.9	28	325	256	9%	IDA	4.1	1286	3.5	13	295	221	3	1.8	1.2	82	80	72	7.1	3	4.1	MILD	II	11
48	Surya	67651	60	M	yes	no	no	yes	8	no	yes	DCLD, cirrhosis, hepatitis B, portal HTN, alcoholism, HE	8.7	2800	70/25/5	2.8	28	91	28	28	0.3	normocytic normochromic cells / 0.8%	1240	30	240	150	13%	ACD	2.8	1690	6	12	28	160	2.4	1	1.4	28	70	96	6.8	3	3.8	MOD	III	12
49	Swaminathan	67743	48	M	no	no	no	yes	4	no	no	cirrhosis ? Cause ? NASH, portal HTN, HE	9.2	4500	80/20	3.3	32	89	26	28	0.8	normocytic normochromic cells / 0.8%	280	60	180	100	30%	ACD	4.2	980	4	6	285	216	1	0.5	0.5	64	90	160	6.8	2.8	4	MILD	I	10
50	Badri		56	M	yes	yes	no	yes	7	no	yes	ALD, cirrhosis, portal HTN, HE	8.8	3800	80/20	3.1	32	110	25	28	0.46	MACROCYTIC PICTURE	860	40	240	150	17%	ACD	2.8	1500	6	14	295	124	3.6	2	1.6	88	110	140	7	3	4	MOD	III	13

KEY TO MASTER CHART

Hb	–	Haemoglobin
TC	–	Total count
DC	–	Differential count
PLT	–	platelet
PCV	–	packed cell volume
MCV	–	mean corpuscular volume
MCH	–	mean corpuscular haemoglobin
MCHC	–	mean corpuscular haemoglobin concentration
TIBC	–	total iron binding capacity
T Sat	–	transferrin saturation
BT	–	bleeding time
PT-INR	–	Prothrombin time - International Normalized Ratio
APTT	–	activated partial thromboplastin time
TB	–	total bilirubin
DB	–	direct bilirubin
IB	–	indirect bilirubin
SGOT	–	serum glutamate oxalate transferase
SGPT	–	serum glutamate Pyruvate transferase
ALP	–	alkaline phosphatase
TP	–	total protein
Alb	–	albumin
Glob	–	globulin